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Support for mid-life anxiety diagnosis as an independent risk factor for dementia: a systematic review.

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Abstract

Objectives: Anxiety is an increasingly recognised predictor of cognitive deterioration in older adults and those with mild cognitive impairment (MCI). Often believed to be a prodromal feature of neurodegenerative disease, anxiety in mid-life and older age may potentially act as an independent risk factor for dementia.

Design: A systematic review of the literature on anxiety diagnosis and long-term risk for dementia was performed following published guidelines.

Setting and participants: Electronic databases were searched for peer-reviewed journals up until 8 March 2017. Publications reporting hazard/odds ratios for all-cause dementia based on clinical criteria from prospective cohort or case-control studies were selected. Included studies measured clinically significant anxiety in isolation or after controlling for symptoms of depression, and reported a mean interval between anxiety assessment and dementia diagnosis of at least 10 years. Methodological quality assessments were performed using the Newcastle-Ottawa scale.

Outcome measure: HR/ORs for all cause dementia.

Results Searches yielded 3510 articles, of which four (0.02%) were eligible. The studies had a combined sample size of 29,819, and all studies found a positive association between clinically significant anxiety and future dementia. Due to the heterogeneity between studies, a meta-analysis was not conducted.

Conclusions Clinically significant anxiety in mid-life was associated with an increased risk of dementia over an interval of at least 10 years. These findings indicate that anxiety may be a risk factor for late-life dementia. With increasing focus on identifying modifiable risk factors

for dementia, more high quality prospective studies are required to clarify whether clinical anxiety is a risk factor for dementia, separate from a prodromal symptom.

Strengths and limitations of this study:

- This systematic review used a rigorous methodology, with broad search terms and precisely pre-defined inclusion and exclusion criteria to investigate a life-course association between a potentially modifiable risk factor, anxiety, and dementia.
- Strict exclusion criteria were used to remove studies that did not either discuss anxiety diagnosis alone or control for depression, to account for high levels of anxiety-depression comorbidity
- Study quality was formally investigated using the Newcastle-Ottawa scale
- The review was limited by the lack of assessment of cognition at baseline in retrospective studies, however, the length of look-back, minimises the likelihood of cognitive impairment at baseline
- The small number and heterogeneity of study designs rendered a meta-analysis inappropriate, therefore formal statistical analyses could not be performed

Introduction

Dementia, and more specifically Alzheimer's disease (AD), is a progressive neurocognitive disease. In the absence of any disease modifying treatments, there is increasing focus on primary prevention to reduce risk of its development, and on early intervention to potentially slow the progression of dementia. A better understanding of risk factors for dementia is therefore vital for improving therapeutic interventions. Alongside a number of well described cardiovascular risk factors [1] increasing evidence has highlighted the

association between psychiatric illnesses and the development of late-onset dementia (Marchant & Howard, 2015). Further work is needed to understand whether these psychiatric symptoms and illnesses represent prodromal symptoms or act as independent risk factors. Depression has been consistently related to the development of dementia [2]. Three meta-analyses have reported that a diagnosis of depression is associated with up to a twofold increase in risk for dementia [2–4]. Ownby and colleagues further report that a longer interval between diagnosis of depression and diagnosis of dementia is significantly associated with an increased odds ratio (OR) of developing dementia. This substantiates interpretations of depression as a risk factor for developing dementia, whereas a stronger association over shorter intervals would have been more indicative of prodromal symptoms [2], however a recent study opposes this [5].

Although anxiety is a prevalent psychiatric disorder [6] and commonly co-occurs with depression, the impact of anxiety on risk for cognitive decline and dementia has been far less studied. Anxiety symptoms are commonly experienced in the years preceding a dementia diagnosis [7], and have been associated with cognitive decline and the progression from MCI to AD [8–10]. A recent review reported that anxiety and neuropsychiatric symptoms not reaching clinically diagnostic levels were associated with increased risk of dementia [11]. The authors indicated that anxiety was likely a prodromal symptom of dementia in these community samples. This may well have been the case, particularly given the relatively short intervals between assessment of anxiety symptoms and assessment of dementia, however, this does not preclude anxiety also being a risk factor. This could more easily be investigated with longer intervals between anxiety assessment and dementia diagnosis, as the studies that have investigated this association within a 5-10 year interval have reported variable results [12,13].

The average length of prodromal preclinical cognitive decline has been proposed to be between 5-6 years [14], and individuals diagnosed with MCI may progress to AD within 5 years [15]. Therefore, examining studies with at least a 10-year interval between anxiety assessment and dementia diagnosis would increase likelihood that anxiety is independent from the dementia prodrome.

It is possible that anxiety symptoms meeting diagnostic threshold will have a stronger association with dementia than general symptoms because this has been shown with depression [3]. To date, there has been no systematic review to investigate the association between clinically significant anxiety and dementia. The aim of this study was therefore to review the literature examining the association between clinically significant levels of anxiety and dementia risk over a longer timescale (>10 years).

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care [16].

Search strategy

A systematic literature search of MEDLINE, PSYCINFO and EMBASE databases was conducted of articles published up until 8th March 2017 to identify articles reporting analyses of the association between anxiety (as defined by clinical diagnosis or self-report scales with a clinically significant threshold) and dementia or MCI incidence. Search terms used consisted of: (dement* OR Alzheimer* OR “mild cognitive impairment” OR MCI) AND (anx* OR “generalised anxiety disorder” OR GAD) AND (risk* OR odds). We aimed to identify articles discussing (1) diagnosis of any type of dementia or MCI, (2) anxiety diagnosis, and

(3) risk of dementia. The search was restricted to human studies and those published in English. Reference lists were searched for additional relevant articles. Searches were conducted by a single reviewer (AG). An independent review of all screened articles was conducted by a second reviewer (MS). Any disagreement was resolved by consensus with a third reviewer (NM).

Selection Criteria and Article Screening

Inclusion criteria were 1) a diagnosis of anxiety or an assessment of anxiety symptoms meeting diagnostic criteria using a standardised assessment tool, excluding populations with post-traumatic stress disorder (PTSD) or obsessive-compulsive disorder (OCD); 2) population-based studies where anxiety is assessed at least – on average – 10 years preceding final clinical assessment for dementia in line with previous meta-analyses on depression using intervals of at least 10 years [2]; 3) a diagnosis of dementia using validated criteria (e.g. Diagnostic Statistical Manual III-IV (DSM III-IV), International Classification of Diseases 10 (ICD-10)); 4) late-onset dementia diagnoses (aged ≥65 years). Eligible articles were identified by performing an initial screen of titles and abstracts, followed by a full article review of those that passed screening. All retrospective and prospective studies that met these criteria were selected.

Data extraction

Outcome measures related to anxiety and dementia diagnosis were independently extracted by two authors (AG, MS). Disagreements were resolved through discussion. Study design, sample characteristics (including educational level and age), follow-up length, dropout rate, anxiety (including measure and baseline score where appropriate), criteria for assessing dementia, and measurements of depression as a confounder (including measure

and baseline score), were recorded. In cases of insufficient data, authors were contacted by email.

INSERT FIGURE 1

Study Quality

Two authors (AG, MS) independently assessed study quality and risk of bias using the Newcastle-Ottawa scale, which contains separate quality assessment instruments for case-control and cohort studies.

Results

Literature Search

The literature search detected 3509 citations, of which two were duplicates. One further paper was identified manually during reference screening. After screening titles and abstracts, 18 full-text articles were assessed for eligibility. Fourteen articles were excluded based on criteria described earlier (Figure 1), four studies were included in the final review.

Study Characteristics

Characteristics of the four selected studies are shown in Table 1. Clinically significant anxiety was documented based on clinical diagnosis using International Classification of Diseases 10 (ICD-10) criteria (n = 2), the State Trait Anxiety Inventory (STAI, n = 1) and a subscale of the State Trait Personality Inventory (STPI, n = 1).

Gallacher et al. (2009) measured anxiety using the STAI, which has a range from 20 to 80 [17]. This questionnaire is arguably the gold standard for assessing anxiety symptoms. A clinically significant cut-off of 39-40 has been proposed [18,19]. Gallacher et al. (2009) categorised 'high anxiety' as having a STAI score between 35 and 72, compared to a 'low

anxiety' group who had a STAI score between 20 and 34. Boot et al. (2013) and Zilkens et al. (2014) used ICD-10 criteria to diagnose an anxiety disorder.

Petkus et al. (2016) assessed anxiety using state anxiety subscale of the State-Trait Personality Inventory (STPI), which contains a subset of items from the STAI. Participants scoring at least one standard deviation above the population mean, equating to a score of ≥25 out of 40, were categorised having 'high anxiety'. This cut-off indicated clinically significant anxiety, therefore rendering the study suitable for inclusion in this review.

Dementia diagnosis was in most cases assessed using DSM III-IV (n = 2) or ICD-10 criteria (n = 1), although the study by Boot et al. (2013) assessed Dementia with Lewy Bodies (DLB) by clinical diagnosis using published criteria [20].

Sample sizes of the studies ranged from 441 to 27 136 participants, recruited from both or either community and hospital inpatient/outpatient populations. Gallacher et al. (2009) and Petkus et al. (2016) conducted prospective cohort studies using community populations that excluded dementia at baseline. Zilkens et al. (2014), and Boot et al. (2013) conducted matched case-control studies, which analysed community and hospital records for anxiety diagnosis and therefore did not include a cognitive assessment at baseline to exclude dementia. The proportion of females in each study ranged from 0 to 56.6%. Educational level was recorded for all but one study; which ranged from 55% with no qualifications to 95% with >9 years of education.

INSERT TABLE 1

Anxiety diagnosis association with dementia

All studies included in this review found a significant increase in the number of dementia diagnoses in patients who had a clinical anxiety diagnosis or experienced clinically significant

anxiety symptoms on average at least 10 years prior to their diagnosis of dementia; Zilkens et al. (2014): OR = 1.61 (95% CI 1.28-2.02), Boot et al. (2013): OR = 7.4 (95% CI 3.5-16), Gallacher et al. (2009): OR = 1.62 (95% CI 0.59-4.41) and Petkus et al. (2016): OR = 1.48 (95% CI 1.01-2.18), respectively.

Each study controlled for a range of demographic factors, with all controlling for vascular and other psychiatric risk factors (Table 2 and 3). All studies assessed and controlled for depression symptoms in their analysis. Boot et al. (2013) found a stronger association between anxiety diagnosis alone with future dementia than either depression diagnosis alone or mixed anxiety and depression diagnosis, although the number of individuals with anxiety was markedly larger than those in the other two categories (anxiety alone n=168; depression alone n=52; anxiety and depression n=56). Although Zilkens et al. (2014) assessed a range of psychiatric diagnoses including anxiety and depression, they did not assess their interaction. Petkus et al. (2016) and Gallacher et al. (2009), whilst controlling for depression, made no assessment of the comparative strength of relationship or their interaction.

Study Quality Rating

All studies included were rated highly on the Newcastle-Ottawa scale [21]. From a maximum score of 9, Boot et al (2013) was rated 8; and Zilkens et al. (2014), Petkus et al. (2016) and Gallacher et al. (2009) were each rated 7. These studies were of similar quality to those included in a recent meta-analysis examining dementia risk estimates associated with late-life depression [3].

Three of the studies had representative samples of community populations; the fourth led by Gallacher et al. (2009) included only men. All controlled for a range of both demographic,

physical and psychological health factors. All outcomes were assessed either via secure health records, or independent validation. Gallacher et al. (2009) experienced 20% loss to follow-up, which compares favourably to the pre-mentioned Cherbuin et al. (2015) review which considered studies with an attrition rate of between 4.3% and 55.46%, and a review of MCI drug studies with attrition rates varying from 12% to 49% [22]. Petkus et al. (2016) did not clearly report loss to follow-up. For both case-control studies, the primary care records did not include a cognitive assessment at baseline. Therefore, pre-existing cognitive impairment before diagnosis cannot be ruled out, although long look-back periods make this less likely.

INSERT TABLE 2

INSERT TABLE 3

Discussion

We systematically reviewed evidence for a relationship between clinically significant anxiety and risk of late-onset dementia over a mean interval of at least 10 years from anxiety assessment to dementia diagnosis. Four studies met inclusion criteria, and each were of high quality. All studies found an association between clinically significant anxiety and increased likelihood of a dementia diagnosis, even after accounting for potential confounders (including depression symptoms).

Anxiety symptomatology has previously been related to dementia risk and cognitive decline, although not conclusively [9,23]. A recent systematic review reported a positive association between anxiety symptoms and dementia diagnosis over a short time interval [11]. Further, the association was stronger with smaller intervals between assessment of anxiety and dementia diagnosis. As a result, the authors concluded that anxiety may result from a

prodromal state of dementia, where an increase in anxiety may be due to an individual's insight into their early, subjective experience of cognitive decline [11]. Given the short time interval between assessments, Gulpers et al. were unable to determine whether anxiety could also serve as an independent risk for dementia. This review reports solely articles that were not included Gulpers et al.'s analyses, and therefore furthers their work by providing an independent assessment of the anxiety-dementia association.

The prodromal phase of dementia can begin several years before objective dementia is manifest. In the present review, we sought to minimise the potential influence of pre-clinical cognitive decline by including only studies that assessed anxiety and dementia diagnoses over an extended period. Three studies (Zilkens et al. 2014; Gallacher et al. 2009; Petkus et al. 2016) demonstrated a mean interval of at least 10 years between the anxiety and dementia evaluations. Boot et al. (2013) analysed participant's lifelong medical record, however, the mean interval between anxiety and dementia diagnosis was not reported. The results summarised here suggest that anxiety may also be an independent risk for dementia.

Findings from this review corroborate recent evidence that anxiety symptoms or diagnosis are associated with risk of MCI [28,29]. These findings further complement the association between depression and dementia diagnosis [3], which is particularly relevant due to high levels of anxiety-depression comorbidity. Moreover, they lend support for the proposal that multiple psychiatric risk factors are implicated together as a latent risk factor for dementia [30].

It has recently been suggested that a longer interval period between anxiety and dementia diagnosis may provide evidence for a common biological pathway linking anxiety, depression, and dementia [26]. An abnormal stress response, such as exhibited in anxiety

disorders, may be associated with accelerated cellular ageing and neuro-progression (a pathological reorganisation of the central nervous system) resulting in increased neurodegeneration, neuronal apoptosis and lowered neuroplasticity [31]. Although glucocorticoid, inflammatory mediator and vascular disease mechanisms are hypothesised [2,32], as yet, no convincing candidate biological mechanism linking anxiety and cognitive impairment exists.

The results of this review should be interpreted in the light of their limitations. Only studies that had been published and written in English were included, which may limit extrapolation across broader populations. Retrospective studies did not examine baseline cognition and therefore cannot exclude early cognitive decline at the time of anxiety assessment, however, the length of look-back, ranging from over 10 years to the first entry of an individual's medical record, minimises the likelihood of cognitive impairment at baseline. To account for high levels of anxiety-depression comorbidity, this review included only papers discussing anxiety diagnosis alone, or those that controlled for depression symptomatology. However, the Zilkens et al. (2014) and Boot et al. (2013) cannot completely exclude overlap of these two commonly comorbid illnesses because their occurrence was ascertained from lists of diagnoses in medical records. Furthermore, results must be interpreted in the light of proposals that the prodromal AD pathophysiologic processes may develop beyond 10 years before the onset of clinical symptoms [33].

Whether reducing anxiety in middle-age would result in reduced risk of dementia remains an open question. The effect of treatment of anxiety using pharmacologic and non-pharmacologic therapies during midlife on later risk for dementia has not yet been investigated. Benzodiazepines, commonly used in the treatment of anxiety, have been

shown to increase risk of mortality in some groups [34]. It is possible that diverse non-pharmacological therapies, including talking therapies [35] and mindfulness-based interventions and meditation practices [36], that are known to reduce anxiety in midlife, could have a risk-reducing effect, although this is yet to be thoroughly researched.

Given the high prevalence of anxiety seen in primary care, we suggest that general practitioners could consider anxiety alongside depression as an indicator of risk factor for dementia. To improve the rate of earlier diagnosis of dementia, close monitoring of subtle cognitive decline in older adults with a history of anxiety, depression and cerebrovascular disease would be encouraged. This review expands our understanding of anxiety as a potentially modifiable risk for dementia. Given the limited number of studies investigating the anxiety-dementia relationship, further research is required to assess underlying mechanisms that link these disorders, and to disambiguate anxiety's potential role as a risk factor as separate from a prodromal symptom of dementia.

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Contributors

AG contributed to design of the study, data screening and extraction, drafting of the manuscript and submission. MS contributed to literature search, data screening and extraction, and manuscript preparation. JDH contributed to the study design, provided methodological expertise and editing of the manuscript. NLM contributed to the conception and study design, data interpretation, and editing of the manuscript.

Competing interests

None of the contributing authors have any conflicting interests to declare.

Data sharing statement

No additional data are available.

References

[1] Fillit H, Nash D, Rundek T, Zuckerman A. Cardiovascular risk factors and dementia. Am J Geriatr Pharmacother 2008;6:100–18.

[2] Ownby R, Crocco E, Acevedo A, John V, Loewenstein D. Depression and Risk for Alzheimer Disease: a systematic review, meta-analysis and metaregression analysis. Arch Gen Psychiatry 2006;63:530.

[3] Cherbuin N, Kim S, Anstey KJ. Dementia risk estimates associated with measures of depression: a systematic review and meta-analysis. BMJ Open 2015;5:e008853.

[4] Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF, Byers A, et al. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry 2013;202:329–35.

[5] Singh-Manoux A, Dugravot A, Fournier A, Abell J, Ebmeier K, Kivimäki M, et al. Trajectories of Depressive Symptoms Before Diagnosis of Dementia. JAMA Psychiatry 2017;74:712.

[6] Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci 2015;17:327–35.

[7] Gallagher D, Coen R, Kilroy D, Belinski K, Bruce I, Coakley D, et al. Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. Int J Geriatr Psychiatry 2011;26:166–72.

[8] Palmer K, Berger AK, Monastero R, Winblad B, Backman L, Fratiglioni L. Predictors

of progression from mild cognitive impairment to Alzheimer disease. Neurology 2007;68:1596–602.

[9] Yochim BP, Mueller AE, Segal DL. Late life anxiety is associated with decreased memory and executive functioning in community dwelling older adults. J Anxiety Disord 2013;27:567–75.

[10] Beaudreau SA, O'Hara R. Late-life anxiety and cognitive impairment: a review. Am J Geriatr Psychiatry 2008;16:790–803.

[11] Gulpers B, Ramakers I, Hamel R, Kohler S, Voshaar R, Verhey F. Anxiety as a Predictor for Cognitive Decline and Dementia: A Systematic Review and Meta-analysis. Am J Geriatr Psychiatry 2016.

[12] de Bruijn RFAG, Direk N, Mirza SS, Hofman A, Koudstaal PJ, Tiemeier H, et al. Anxiety is not associated with the risk of dementia or cognitive decline: the Rotterdam Study. Am J Geriatr Psychiatry 2014;22:1382–90.

[13] Burton C, Campbell P, Jordan K, Strauss V, Mallen C. The association of anxiety and depression with future dementia diagnosis: A case-control study in primary care. Fam Pract 2013;30:25–30.

[14] Wilson RS, Leurgans SE, Boyle PA, Bennett DA. Cognitive decline in prodromal Alzheimer disease and mild cognitive impairment. Arch Neurol 2011;68:351–6.

[15] Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. Lancet 2006;367:1262–70.

[16] Centre for Reviews and Dissemination. CRD's Guidance for undertaking reviews in health care. 2009.

[17] Spielberger C. Manual for the State-Trait Anxiety Inventory. 1983.

[18] Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Arthritis Care Res (Hoboken) 2011:S467-72.

[19] Knight RG, Waal-Manning HJ, Spears GF. Some norms and reliability data for the State-Trait Anxiety Inventory and the Zung Self-Rating Depression scale. Br J Clin Psychol 1983;22:245–9.

[20] McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: Third report of the DLB consortium. Neurology 2005;65:1863–72.

[21] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. (Available from URL Http//www.ohri.ca/programs/clinical_epidemiology/oxford.asp) 2012:2012.

[22] Jelic V, Kivipelto M, Winblad B. Clinical trials in mild cognitive impairment: lessons for the future. J Neurol Neurosurg Psychiatry 2006;77:429–38.

[23] Bierman EJM, Comijs HC, Rijmen F, Jonker C, Beekman ATF. Anxiety symptoms and cognitive performance in later life: results from the longitudinal aging study

Amsterdam. Aging Ment Health 2008;12:517–23.

[24] Zilkens RR, Bruce DG, Duke J, Spilsbury K, Semmens JB. Severe psychiatric disorders in mid-life and risk of dementia in late-life (age 65-84 years): A population based case-control study. Curr Alzheimer Res 2014;11:681–93.

[25] Boot BP, Orr CF, Ahlskog JE, Ferman TJ, Roberts R, Pankratz VS, et al. Risk factors for dementia with Lewy bodies: a case-control study. Neurology 2013;81:833–40.

[26] Gallacher J, Bayer A, Fish M, Pickering J, Pedro S, Dunstan F, et al. Does anxiety affect risk of dementia? Findings from the Caerphilly Prospective Study. Psychosom Med 2009;71:659–66.

[27] Petkus AJ, Reynolds CA, Wetherell JL, Kremen WS, Pedersen NL, Gatz M, et al. Anxiety is associated with increased risk of dementia in older Swedish twins. Alzheimer's Dement 2016;12:399–406.

[28] Jacob L, Bohlken J, Kostev K. Risk Factors for Mild Cognitive Impairment in German Primary Care Practices. J Alzheimer's Dis 2017;56:379–84.

[29] Kassem AM, Ganguli M, Yaffe K, Hanlon JT, Lopez OL, Wilson JW, et al. Anxiety symptoms and risk of dementia and mild cognitive impairment in the oldest old women. Aging Ment Health 2017:1–9.

[30] Marchant NL, Howard RJ. Cognitive debt and Alzheimer's disease. J Alzheimers Dis 2015;44:755–70.

[31] Perna G, Iannone G, Alciati A, Caldirola D. Are Anxiety Disorders Associated with Accelerated Aging? A Focus on Neuroprogression. Neural Plast 2016;2016:1–19.

[32] Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925–35.

[33] Pietrzak RH, Lim YY, Neumeister A, Ames D, Ellis KA, Harrington K, et al. Amyloid-β, anxiety, and cognitive decline in preclinical Alzheimer disease: a multicenter, prospective cohort study. JAMA Psychiatry 2015;72:284–91.

[34] Fontanella CA, Campo J V., Phillips GS, Hiance-Steelesmith DL, Sweeney HA, Tam K, et al. Benzodiazepine Use and Risk of Mortality Among Patients With Schizophrenia. J Clin Psychiatry 2016;77:661–7.

[35] Orgeta V, Qazi A, Spector AE, Orrell M. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment. In: Orgeta V, editor. Cochrane Database Syst. Rev., Chichester, UK: John Wiley & Sons, Ltd; 2014.

[36] Khoury B, Lecomte T, Fortin G, Masse M, Therien P, Bouchard V, et al. Mindfulness-based therapy: A comprehensive meta-analysis. Clin Psychol Rev 2013;33:763–71.

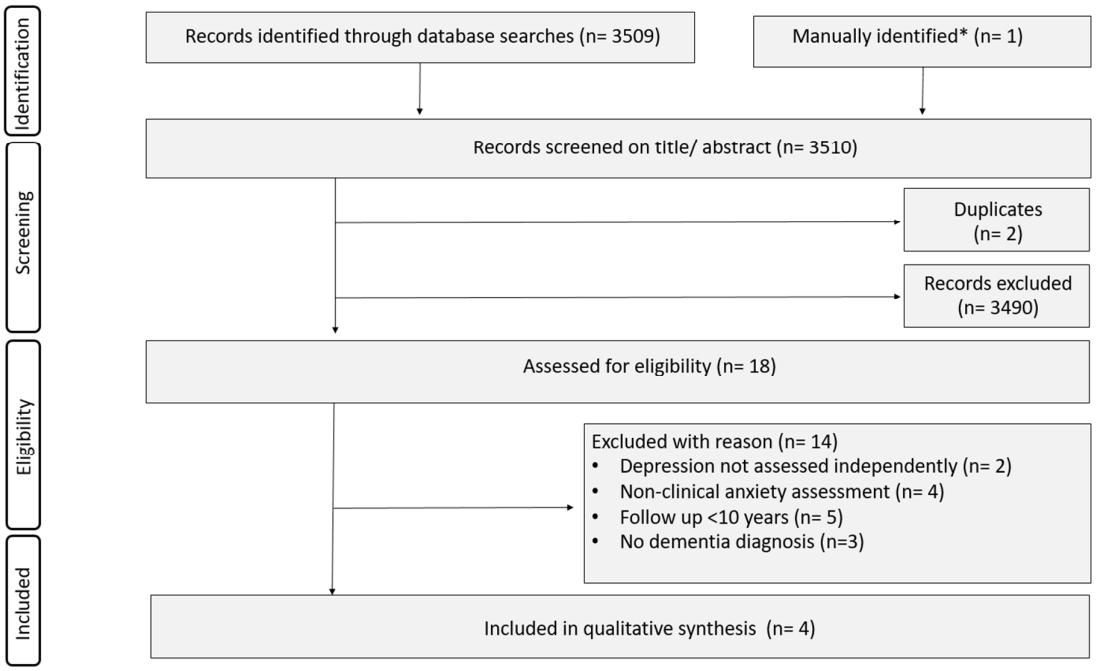

Figure 1 Flowchart of the search and study selection process; * = manually identified from Petkus et al. (2016)

Table 1 Study Characteristics

	Study type and setting; location	Follow-up/ Look back period; years (SD)	Mean age years (SD)	Female n (%)	Education level; no. (%)	Drop-out rate/Non-response rate %	Baseline cognition measure	Anxiety measure; cut-off	Baseline anxiety, %	Controls for depression; baseline depression measure	Dementia diagnosis; criteria (no. cases); OR/HR (95% CI)
Boot et al. 2013 (n=441)	Population based matched case-controlled, Mayo Clinic Rochester, Minnesota, USA	Lifelong diagnoses documented by medical record	72.5 (7.3) – DLB cases age at diagnosis	103 (23.1)	>9 yrs education; (95)	NR	NR	Clinical diagnosis, present in medical history section of medical record	23, 27% cases; 14, 5% controls	Yes; clinical diagnosis from medical history record	DLB diagnosis by behavioural neurologist; published criteria by McKeith et al (2005) (n=147); OR 7.4 (3.5-16)
Gallacher et al. 2009 (n=1160)	Prospective, community based cohort; Caerphilly, Wales, UK	Mean follow up period; 17.3 (1.3)	56.1 (4.4) – mean age at inclusion	0	no qualifications; 601 (55)	20	NR; dementia unlikely at inclusion (mean age <60 yrs)	STAI; score of ≥35	585, 50%	Yes; GHQ-30	Dementia diagnosis; DSM-IV or medical records (n=90); OR 1.62 (0.59-4.41)
Petkus et al. 2016 (n=1082)	Prospective, community based cohort; Swedish twins drawn from Swedish Twin Registry, Sweden	Follow up period; 28 (0)	60.86 (11.15) – mean age at inclusion	612 (56.6)	Beyond elementary education; 423 (39)	29.8	MMSE	State anxiety subscale of STPI; STPI > 1 SD Q1-Q4 (assessments over 4 time-points)	403, 37%	Yes; OARS depression subscale, CES-D	Dementia diagnosis; DSM-III or DMS-IV (n=172); HR 1.48 (1.01-2.18)
Zilkens et al. 2014 (n=27136)	Population based matched case-controlled, Western Australia	Mean look back period; cases 20.4 (10.4), controls 20.0 (10.3)	78.7 (4.7) – mean age at final time point	15359 (56.6)	NR	6.17 (excluded individuals)	NR	Clinical diagnosis using ICD-10 AM (Australian Modification) codes documented in health records; meeting diagnostic threshold	379, 2.8% cases	Yes; clinical diagnosis by GP	Dementia diagnosis; ICD-10 (n=13568); OR 1.61 (1.28-2.02) (>10 years look back period)

(CES-D = Centre of Epidemiological Studies depression subscale, DLB = Dementia with Lewy bodies, GHQ-30 = 30-item general health questionnaire, NR = not recorded; OARS = older American resources and services; STAI = State trait anxiety inventory; STPI = State trait personality inventory)

Table 2 Case controlled studies: Newcastle-Ottawa scale for assessment of quality of included case controlled studies (+ / - represents whether individual criterion within the subsection was fulfilled)

	Acceptable Criteria	**Zilkens et al. 2014**		**Boot et al. 2013**	
Selection					
Case definition	With independent validation	Record linkage from Western Australian Data Linkage System and Death Registry, no independent validation	-	Assessment for DLB using behavioural neurologist	+
Representative-ness of cases	Consecutive or representative series of cases	All dementia cases in period 2000-2009 identified via read-code; lower limit index dementia age 65 years, upper limit 84 years; dementia in other diseases excluded	+	Recruited from longitudinal studies in period 1984-2013 (Alzheimer Disease Patient Registry, Alzheimer Disease Research Centre Study, and Mayo Clinic Study of Ageing); community dwelling persons aged 70-89 years; excluded structural brain lesions	+
Selection of controls	Community controls	Population controls; randomly selected from electoral role aged ≥65 years prior to extraction of health data for controls	+	Community controls from longitudinal study of ageing; individuals aged ≥65 years; selected if seen by physician in same month as clinical subject diagnosed; matched by age and sex	+
Definition of controls	No history of disease	Excluded if dementia read-code in records; no independent screening	+	Excluded if diagnosed with DLB/AD during the study, previous stroke, head injury, neurologic disease or movement disorder; extensive cognitive and medical examination	+
Comparability					
Comparability of cases and controls on basis of design and analysis	Study controls for the most important factor (+/-), and any additional factor (+/-)	Controls for age, sex, vascular risk factors (diabetes, IHD, AF, CVD, hypertension, hyperlipidaemia, heart failure and past or current smoking), head injury, alcohol dependence syndrome, and depression	+ +	Controls for age, sex; multivariate analyses control for family history, depression, APOE ε4 alleles, education level, head injury, cancer, and vascular risk factors (stroke, diabetes, alcohol, smoking)	+ +
Exposure					
Ascertainment of exposure	Secure record, structured interview by healthcare practitioner	Secure administrative health record, read-codes for mid-life factors documented between aged 30-65 years within years 1966-2009	+	Anxiety history from medical history section of medical record	+
Same method of ascertainment for cases and controls	Yes	Yes; review of risk factor read-codes	+	Yes; review of medical history	+
Non-response rate	Similar for both cases and controls	NR	-	NR	-
Total Score			**7**		**8**

(DLB = Dementia with Lewy bodies; NR = not recorded)

Table 3 Cohort studies: Newcastle-Ottawa scale for assessment of quality of included cohort studies (+ / - represents whether individual criterion within the subsection was fulfilled)

	Acceptable Criteria	Petkus et al. 2016		Gallacher et al. 2009	
Selection					
Representative ness of exposed cohort	Representative of average adult in the community (age/sex)	Population based Swedish twin registry, subsample of twins aged ≥ 50 years	+	Men only, representative of male inhabitants of Caerphilly region	-
Selection of non-exposed cohort	Drawn from same community as exposed cohort	Drawn from same community as exposed cohort	+	Drawn from same community as exposed cohort	+
Ascertainment of exposure	Secured records, clinical diagnosis using diagnostic tools (ICD-10/DSM-V)	State anxiety subscale of the State-Trait Personality Inventory (STPI), containing a subset of items from the STAI	+	Structured interview using STAI	+
Demonstration that outcome of interest was not present at start of study	Assessment for dementia at initial enrolment	No baseline screening, exclusion if previous dementia diagnosis, age at inclusion (mean age 60.86 years) makes cognitive impairment unlikely	-	Age at inclusion (mean age 56.1 years) makes cognitive impairment unlikely	-
Comparability					
Comparability of cohorts on basis of design or analysis	Study controls for the most important factor (+), and for any additional factor (+)	Multivariate models control for depression symptoms, baseline age, sex, education, physical illness	+ +	Study controls for age, social class, marital status, vascular risk factors (alcohol consumption, BP, BMI, total cholesterol, previous vascular disease), educational ability (National Adult Reading Test), and depression symptoms (GHQ-30)	+ +
Exposure					
Assessment of outcome	Independent blind assessment, record linkage	Screening for dementia using MMSE, cognitive in-person testing (assessing a range of cognitive domains), DSM-III or IV, and record linkage using National Patient Registry and National Patient Cause of Death Registry	+	Cognitive function assessed using CAMDEX, FAB, CDR; diagnosis made using DSM-IV, screening of primary care and hospital records	+
Follow up adequate for outcome to occur	Follow up >10 years	28 years	+	>20 years	+
Adequacy of follow up of cohorts	Complete follow up, or subjects lost to follow-up unlikely to introduce bias	NR	-	20% lost to follow up	+
Total Score			**7**		**7**

(BMI = body mass index; BP = blood pressure; CAMDEX = Cambridge mental disorders of the elderly examination; CDR = clinical dementia rating; DSM III/IV/V = Diagnostic and statistical manual of mental disorders III/IV/V; FAB = frontal assessment battery; GHQ-30 = 30-item general health questionnaire; ICD-10 = International classification of diseases 10; MMSE = mini mental state examination; NR = not recorded; STAI = State trait anxiety inventory)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2, 9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7,17
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6,7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10,19,20
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10,19,20
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8,9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12,13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11,12,13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Support for mid-life anxiety diagnosis as an independent risk factor for dementia: a systematic review.

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Support for mid-life anxiety diagnosis as an independent risk factor for dementia: a systematic review.

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Abstract

Objectives: Anxiety is an increasingly recognised predictor of cognitive deterioration in older adults and those with mild cognitive impairment (MCI). Often believed to be a prodromal feature of neurodegenerative disease, anxiety may also be an independent risk factor for dementia, operationally defined here as preceding dementia diagnosis by >10 years.

Design: A systematic review of the literature on anxiety diagnosis and long-term risk for dementia was performed following published guidelines.

Setting and participants: MEDLINE, PSYCINFO, and EMBASE were searched for peer-reviewed journals up until 8 March 2017. Publications reporting hazard/odds ratios for all-cause dementia based on clinical criteria from prospective cohort or case-control studies were selected. Included studies measured clinically significant anxiety in isolation or after controlling for symptoms of depression, and reported a mean interval between anxiety assessment and dementia diagnosis of at least 10 years. Methodological quality assessments were performed using the Newcastle-Ottawa scale.

Outcome measure: HR/ORs for all cause dementia.

Results Searches yielded 3510 articles, of which four (0.02%) were eligible. The studies had a combined sample size of 29,819, and all studies found a positive association between clinically significant anxiety and future dementia. Due to the heterogeneity between studies, a meta-analysis was not conducted.

Conclusions Clinically significant anxiety in mid-life was associated with an increased risk of dementia over an interval of at least 10 years. These findings indicate that anxiety may be a risk factor for late-life dementia, excluding anxiety that is related to prodromal cognitive decline. With increasing focus on identifying modifiable risk factors for dementia, more high

quality prospective studies are required to clarify whether clinical anxiety is a risk factor for dementia, separate from a prodromal symptom.

Strengths and limitations of this study:

- This systematic review used a rigorous methodology, with broad search terms and precisely pre-defined inclusion and exclusion criteria to investigate a life-course association between a potentially modifiable risk factor, anxiety, and dementia, whilst excluding anxiety related to pre-clinical dementia.
- Strict exclusion criteria were used to remove studies that did not either discuss anxiety diagnosis alone or control for depression, to account for high levels of anxiety-depression comorbidity
- Study quality was formally investigated using the Newcastle-Ottawa scale
- The review was limited by the lack of assessment of cognition at baseline in retrospective studies, however, the length of look-back minimises the likelihood of cognitive impairment at baseline
- The small number and heterogeneity of study designs rendered a meta-analysis inappropriate, therefore formal statistical analyses could not be performed

Introduction

Dementia, and more specifically Alzheimer's disease (AD), is a progressive neurocognitive disease. In the absence of any disease modifying treatments, there is increasing focus on primary prevention to reduce risk of its development, and on early intervention to potentially slow progression. A better understanding of risk factors for dementia is therefore vital for improving therapeutic interventions. Alongside a number of well

described cardiovascular risk factors [1], increasing evidence has highlighted the association between psychiatric illnesses and the development of late-onset dementia [2]. Further work is needed to understand whether these psychiatric symptoms and illnesses represent prodromal symptoms or act as independent risk factors.

Depression has been consistently related to the development of dementia [3]. Three meta-analyses have reported that a diagnosis of depression is associated with up to a twofold increase in risk [3–5]. Ownby and colleagues further report that a longer interval between diagnosis of depression and diagnosis of dementia is significantly associated with an increased odds ratio (OR) of developing dementia [3]. This substantiates interpretations of depression as a risk factor for developing dementia, whereas a stronger association over shorter intervals would have been more indicative of prodromal symptoms. Conversely, a recent study found no association between dementia and depressive symptoms experienced more than 22 years before dementia diagnosis, however a positive association between dementia and depressive symptoms experienced on average 11 years prior to diagnosis of dementia was reported [6].

Although anxiety is a prevalent psychiatric disorder [7], and commonly co-occurs with depression, the impact of anxiety on risk for cognitive decline and dementia has been far less studied. Anxiety symptoms are commonly experienced in the years preceding a dementia diagnosis [8], and have been associated with cognitive decline and the progression from MCI to AD [9–11]. A recent review reported that anxiety and neuropsychiatric symptoms not reaching clinically diagnostic levels were associated with increased risk of dementia [12]. The authors indicated that anxiety was likely a prodromal symptom of dementia in these community samples. This may well have been the case,

particularly given the relatively short intervals between assessment of anxiety symptoms and assessment of dementia, however, this does not preclude anxiety also being a risk factor.

The association between anxiety symptoms (independent of the dementia-prodrome) and dementia in later life could more easily be investigated with longer intervals between anxiety assessment and dementia diagnosis, as the studies that have investigated this association within a 5-10 year interval have reported variable results [13,14]. The average length of prodromal preclinical cognitive decline has been proposed to be between 5-6 years [15], and individuals diagnosed with MCI may progress to AD within 5 years [16]. Therefore, examining studies with at least a 10-year interval between anxiety assessment and dementia diagnosis would increase likelihood that anxiety is independent from the dementia prodrome.

It is possible that anxiety symptoms meeting diagnostic threshold will have a stronger association with dementia than general symptoms because this has been shown with depression [4]. To date, there has been no systematic review to investigate the association between clinically significant anxiety and dementia. The aim of this study was therefore to review the literature examining the association between clinically significant levels of anxiety and dementia risk over a longer timescale (>10 years).

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care [17].

Search strategy

A systematic literature search of MEDLINE, PSYCINFO and EMBASE databases was conducted of articles published from inception up until 8th March 2017 to identify articles reporting analyses of the association between anxiety (as defined by clinical diagnosis or self-report scales with a clinically significant threshold) and dementia or MCI incidence. Search terms used consisted of: (dement* OR Alzheimer* OR "mild cognitive impairment" OR MCI) AND (anx* OR "generalised anxiety disorder" OR GAD) AND (risk* OR odds), as presented in online supplementary table ST1. We aimed to identify articles discussing (1) diagnosis of any type of dementia, (2) anxiety diagnosis, and (3) risk of dementia. The search was restricted to human studies and those published in English. Reference lists were searched for additional relevant articles. Searches were conducted by a single reviewer (AG). An independent review of all screened articles was conducted by a second reviewer (MS). Any disagreement was resolved by consensus with a third reviewer (NM), which occurred in two cases.

Selection Criteria and Article Screening

Inclusion criteria were 1) a diagnosis of anxiety or an assessment of anxiety symptoms meeting diagnostic criteria using a standardised assessment tool, excluding populations with post-traumatic stress disorder (PTSD) or obsessive-compulsive disorder (OCD); 2) population-based studies where anxiety is assessed at least – on average – 10 years preceding final clinical assessment for dementia in line with previous meta-analyses on depression using intervals of at least 10 years [3]; 3) a diagnosis of dementia using validated criteria (e.g. Diagnostic Statistical Manual III-IV (DSM III-IV), International Classification of Diseases 10 (ICD-10)); 4) late-onset dementia diagnoses (aged ≥65 years). Eligible articles were identified by performing an initial screen of titles and abstracts, followed by a full

article review of those that passed screening. All retrospective and prospective studies that met these criteria were selected.

Data extraction

Outcome measures related to anxiety and dementia diagnosis were independently extracted by two authors (AG, MS). Disagreements were resolved through discussion. Study design, sample characteristics (including educational level and age), follow-up length, dropout rate, anxiety (including measure and baseline score where appropriate), criteria for assessing dementia, and measurements of depression as a confounder (including measure and baseline score), were recorded. In cases of insufficient data, authors were contacted by email.

INSERT FIGURE 1

Study Quality

Two authors (AG, MS) independently assessed study quality and risk of bias using the Newcastle-Ottawa scale, which contains separate quality assessment instruments for case-control and cohort studies.

Results

Literature Search

The literature search detected 3509 citations, of which two were duplicates. One further paper was identified manually during reference screening. After screening titles and abstracts, 18 full-text articles were assessed for eligibility. Fourteen articles were excluded based on criteria described earlier (Figure 1), four studies were included in the final review [18–21].

Study Characteristics

Characteristics of the four selected studies are shown in Table 1. Clinically significant anxiety was documented based on clinical diagnosis using International Classification of Diseases 10 (ICD-10) criteria (n = 2), the State Trait Anxiety Inventory (STAI, n = 1) and a subscale of the State Trait Personality Inventory (STPI, n = 1).

Gallacher et al. (2009) measured anxiety using the STAI, which has a range from 20 to 80 [22], and is a validated measure for assessing anxiety symptoms. A clinically significant cut-off of 39-40 has been proposed [23,24]. Gallacher et al. (2009) categorised 'high anxiety' as having a STAI score between 35 and 72, compared to a 'low anxiety' group who had a STAI score between 20 and 34. Boot et al. (2013) and Zilkens et al. (2014) used ICD-10 criteria to diagnose an anxiety disorder.

Petkus et al. (2016) assessed anxiety using state anxiety subscale of the State-Trait Personality Inventory (STPI), which contains a subset of items from the STAI. Participants scoring at least one standard deviation above the population mean, equating to a score of ≥25 out of 40, were categorised having 'high anxiety'**.** Although there is no established cut-off for clinically significant anxiety using this scale, scores greater than 1 SD above the population mean are likely to represent a group with a high anxiety symptom burden. After discussion amongst the reviewers (AG, MS, NLM), we reached a consensus judgement that the study was suitable for inclusion in this review.

Dementia diagnosis was in most cases assessed using DSM III-IV (n = 2) or ICD-10 criteria (n = 1), although the study by Boot et al. (2013) assessed Dementia with Lewy Bodies (DLB) by clinical diagnosis using published criteria [25].

Sample sizes of the studies ranged from 441 to 27 136 participants, recruited from both or either community and hospital inpatient/outpatient populations. Gallacher et al. (2009) and Petkus et al. (2016) conducted prospective cohort studies using a community twin-population that excluded dementia at baseline. Zilkens et al. (2014), and Boot et al. (2013) conducted matched case-control studies, which retrospectively analysed community and hospital records of individuals with dementia or case-matched controls for anxiety diagnosis and therefore did not include a cognitive assessment at baseline to exclude dementia. Zilkens et al. (2014) drew controls from the electoral roll, whereas Boot et al. (2013) drew them from the community-dwelling persons included in the Mayo Clinic Study of Aging. The proportion of females in each study ranged from 0 to 56.6%. Educational level was recorded for all but one study; which ranged from 55% with no qualifications to 95% with >9 years of education.

INSERT TABLE 1

Anxiety diagnosis association with dementia

All studies included in this review found a significant increase in the number of dementia diagnoses in patients who had a clinical anxiety diagnosis or experienced clinically significant anxiety symptoms on average at least 10 years prior to their diagnosis of dementia; Zilkens et al. (2014): OR = 1.61 (95% CI 1.28-2.02), Boot et al. (2013): OR = 7.4 (95% CI 3.5-16), Gallacher et al. (2009): OR = 1.62 (95% CI 0.59-4.41) and Petkus et al. (2016): OR = 1.48 (95% CI 1.01-2.18), respectively [18–21]. On the whole, retrospective studies that looked back for life-long diagnoses of anxiety found a stronger association between mid-life anxiety and later dementia diagnosis, than prospective studies investigating an association over a shorter time period. Additionally, Petkus et al. (2016) demonstrated that the association

between high anxiety and dementia diagnosis remained when they excluded participants who developed dementia within 5 years of the baseline assessment. This subsample had an average interval between baseline and dementia diagnosis of 14.7 years (SD 6.7 years). Both lend support that the associations found were independent of prodromal dementia symptoms.

Each study controlled for a range of demographic factors, with all controlling for vascular and other psychiatric risk factors (Table 2 and 3). All studies assessed and controlled for depression symptoms in their analysis. Boot et al. (2013) found a stronger association between anxiety diagnosis alone with future dementia than either depression diagnosis alone or mixed anxiety and depression diagnosis, although the number of individuals with anxiety was markedly larger than those in the other two categories (anxiety alone n=168; depression alone n=52; anxiety and depression n=56). Although Zilkens et al. (2014) assessed a range of psychiatric diagnoses including anxiety and depression, they did not assess their interaction. Petkus et al. (2016) and Gallacher et al. (2009), whilst controlling for depression, made no assessment of the comparative strength of relationship or their interaction.

Study Quality Rating

All studies included were rated highly on the Newcastle-Ottawa scale [26]. From a maximum score of 9, Boot et al (2013) was rated 8; and Zilkens et al. (2014), Petkus et al. (2016) and Gallacher et al. (2009) were each rated 7. These studies were of similar quality to those included in a recent meta-analysis examining dementia risk estimates associated with late-life depression [4].

Three of the studies had representative samples of community populations; the fourth led by Gallacher et al. (2009) included only men. All controlled for a range of both demographic, physical and psychological health factors. All outcomes were assessed either via secure health records, or independent validation. Gallacher et al. (2009) experienced 20% loss to follow-up, which compares favourably to the pre-mentioned Cherbuin et al. (2015) review, which considered studies with an attrition rate of between 4.3% and 55.46%, and a review of MCI drug studies with attrition rates varying from 12% to 49% [27]. Petkus et al. (2016) did not clearly report loss to follow-up. For both case-control studies, the primary care records did not include a cognitive assessment at baseline. Therefore, pre-existing cognitive impairment before diagnosis cannot be ruled out, although long look-back periods make this less likely.

INSERT TABLE 2

INSERT TABLE 3

Discussion

This systematic review found four high quality studies that all showed a positive association between clinically significant anxiety and risk of late-onset dementia over a mean interval of at least 10 years from anxiety assessment to dementia diagnosis, even after accounting for potential confounders. This important finding provides further evidence that a common mental health condition in mid-life is associated with later life neurodegenerative disorders.

Anxiety symptomatology has previously been related to dementia risk and cognitive decline, although not conclusively [10,28]. A recent systematic review reported a positive association between anxiety symptoms and dementia diagnosis over a short time interval [12]. In that review the majority of studies reported follow up periods between 2-3.8 years.

A single study had a follow up time of up to 11.8 years, however the average interval between anxiety and dementia diagnosis may have been less than 10 years, therefore it was not included in the current review [13]. Gulpers et al. found stronger associations with smaller intervals between assessment of anxiety and dementia diagnosis. As a result, the authors concluded that anxiety may result from a prodromal state of dementia, where an increase in anxiety may be due to an individual's insight into their early, subjective experience of cognitive decline [12]. Given the short time interval between assessments, Gulpers et al. were unable to determine whether anxiety could also serve as an independent risk for dementia. This review reports solely articles that were not included Gulpers et al.'s analyses, and therefore furthers their work by providing an independent assessment of the anxiety-dementia association. Effect sizes of the studies included in this review (1.48 - 7.4) were comparable to the overall effect size found by Gulpers et al. (2016) of 1.61, suggesting that the association between clinically significant mid-life anxiety and later-life dementia is as strong as that between late-life anxiety symptoms and dementia.

The prodromal phase of dementia can begin several years before objective dementia is manifest. In the present review, we sought to minimise the potential influence of pre-clinical cognitive decline by including only studies that assessed anxiety and dementia diagnoses over an extended period. Three studies (Zilkens et al. 2014; Gallacher et al. 2009; Petkus et al. 2016) demonstrated a mean interval of at least 10 years between the anxiety and dementia evaluations. Boot et al. (2013) analysed participant's lifelong medical record, however, the mean interval between anxiety and dementia diagnosis was not reported.

Findings from this review corroborate recent evidence that anxiety symptoms or diagnosis are associated with risk of MCI [29,30]. These findings further complement the association

between depression and dementia diagnosis [4], which is particularly relevant due to high levels of anxiety-depression comorbidity. Moreover, they lend support for the proposal that multiple psychiatric risk factors are implicated together as a latent risk factor for dementia [2].

It has recently been suggested that a longer interval period between anxiety and dementia diagnosis may provide evidence for a common biological pathway linking anxiety, depression, and dementia [20]. An abnormal stress response, such as exhibited in anxiety disorders, may be associated with accelerated cellular ageing and neuro-progression (a pathological reorganisation of the central nervous system) resulting in increased neurodegeneration, neuronal apoptosis and lowered neuroplasticity [31]. Although glucocorticoid, inflammatory mediator and vascular disease mechanisms are hypothesised [3,32], as yet, no convincing candidate biological mechanism linking anxiety and cognitive impairment exists.

The results of this review should be interpreted in the light of their limitations. Only studies that had been published and written in English were included, which may limit extrapolation across broader populations. Retrospective studies did not examine baseline cognition and therefore cannot exclude early cognitive decline at the time of anxiety assessment, however, the length of look-back, ranging from over 10 years to the first entry of an individual's medical record, minimises the likelihood of cognitive impairment at baseline. To account for high levels of anxiety-depression comorbidity, this review included only papers discussing anxiety diagnosis alone, or those that controlled for depression symptomatology. However, the Zilkens et al. (2014) and Boot et al. (2013) cannot completely exclude overlap of these two commonly comorbid illnesses because their occurrence was ascertained from

lists of diagnoses in medical records. The use of read codes in retrospective studies may have resulted in lower identification of individuals with clinically significant anxiety as a result of inconsistent entry of read codes during evaluations, or of absence of clinical record for non-help seekers [33]. Publication bias may also have influenced the studies included, as positive findings may be more likely to have been published than studies finding no association. Furthermore, results must be interpreted in the light of proposals that the prodromal AD pathophysiologic processes may develop beyond 10 years before the onset of clinical symptoms [34].

Whether reducing anxiety in middle-age would result in reduced risk of dementia remains an open question. The effect of treatment of anxiety using pharmacologic and non-pharmacologic therapies during midlife on later risk for dementia has not yet been investigated. Benzodiazepines, commonly used in the treatment of anxiety, have been shown to increase risk of mortality in some groups [35]. It is possible that diverse non-pharmacological therapies, including talking therapies [36] and mindfulness-based interventions and meditation practices [37], that are known to reduce anxiety in midlife, could have a risk-reducing effect, although this is yet to be thoroughly researched.

Given the high prevalence of anxiety seen in primary care, we suggest that general practitioners could consider anxiety alongside depression as an indicator of risk factor for dementia. To improve the rate of earlier diagnosis of dementia, close monitoring of subtle cognitive decline in older adults with a history of anxiety, depression and cerebrovascular disease would be encouraged. This review expands our understanding of anxiety as a potentially modifiable risk for dementia. Given the limited number of studies investigating the anxiety-dementia relationship, further research is required to assess underlying

mechanisms that link these disorders, and to disambiguate anxiety's potential role as a risk factor as separate from a prodromal symptom of dementia.

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Contributors

AG contributed to design of the study, data screening and extraction, drafting of the manuscript and submission. MS contributed to literature search, data screening and extraction, and manuscript preparation. JDH contributed to the study design, provided methodological expertise and editing of the manuscript. NLM contributed to the conception and study design, data interpretation, and editing of the manuscript.

Competing interests

None of the contributing authors have any conflicting interests to declare.

Data sharing statement

No additional data are available.

References

[1] Fillit H, Nash D, Rundek T, Zuckerman A. Cardiovascular risk factors and dementia.

Am J Geriatr Pharmacother 2008;6:100–18.

[2] Marchant NL, Howard RJ. Cognitive debt and Alzheimer's disease. J Alzheimers Dis 2015;44:755–70.

[3] Ownby R, Crocco E, Acevedo A, John V, Loewenstein D. Depression and Risk for Alzheimer Disease: a systematic review, meta-analysis and metaregression analysis. Arch Gen Psychiatry 2006;63:530.

[4] Cherbuin N, Kim S, Anstey KJ. Dementia risk estimates associated with measures of depression: a systematic review and meta-analysis. BMJ Open 2015;5:e008853.

[5] Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF, Byers A, et al. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry 2013;202:329–35.

[6] Singh-Manoux A, Dugravot A, Fournier A, Abell J, Ebmeier K, Kivimäki M, et al. Trajectories of Depressive Symptoms Before Diagnosis of Dementia. JAMA Psychiatry 2017;74:712.

[7] Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci 2015;17:327–35.

[8] Gallagher D, Coen R, Kilroy D, Belinski K, Bruce I, Coakley D, et al. Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. Int J Geriatr Psychiatry 2011;26:166–72.

[9] Palmer K, Berger AK, Monastero R, Winblad B, Backman L, Fratiglioni L. Predictors of progression from mild cognitive impairment to Alzheimer disease. Neurology 2007;68:1596–602.

[10] Yochim BP, Mueller AE, Segal DL. Late life anxiety is associated with decreased memory and executive functioning in community dwelling older adults. J Anxiety Disord 2013;27:567–75.

[11] Beaudreau SA, O'Hara R. Late-life anxiety and cognitive impairment: a review. Am J Geriatr Psychiatry 2008;16:790–803.

[12] Gulpers B, Ramakers I, Hamel R, Kohler S, Voshaar R, Verhey F. Anxiety as a Predictor for Cognitive Decline and Dementia: A Systematic Review and Meta-analysis. Am J Geriatr Psychiatry 2016.

[13] de Bruijn RFAG, Direk N, Mirza SS, Hofman A, Koudstaal PJ, Tiemeier H, et al. Anxiety is not associated with the risk of dementia or cognitive decline: the Rotterdam Study. Am J Geriatr Psychiatry 2014;22:1382–90.

[14] Burton C, Campbell P, Jordan K, Strauss V, Mallen C. The association of anxiety and depression with future dementia diagnosis: A case-control study in primary care. Fam Pract 2013;30:25–30.

[15] Wilson RS, Leurgans SE, Boyle PA, Bennett DA. Cognitive decline in prodromal Alzheimer disease and mild cognitive impairment. Arch Neurol 2011;68:351–6.

[16] Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild

cognitive impairment. Lancet 2006;367:1262–70.

[17] Centre for Reviews and Dissemination. CRD's Guidance for undertaking reviews in health care. 2009.

[18] Zilkens RR, Bruce DG, Duke J, Spilsbury K, Semmens JB. Severe psychiatric disorders in mid-life and risk of dementia in late-life (age 65-84 years): A population based case-control study. Curr Alzheimer Res 2014;11:681–93.

[19] Boot BP, Orr CF, Ahlskog JE, Ferman TJ, Roberts R, Pankratz VS, et al. Risk factors for dementia with Lewy bodies: a case-control study. Neurology 2013;81:833–40.

[20] Gallacher J, Bayer A, Fish M, Pickering J, Pedro S, Dunstan F, et al. Does anxiety affect risk of dementia? Findings from the Caerphilly Prospective Study. Psychosom Med 2009;71:659–66.

[21] Petkus AJ, Reynolds CA, Wetherell JL, Kremen WS, Pedersen NL, Gatz M, et al. Anxiety is associated with increased risk of dementia in older Swedish twins. Alzheimer's Dement 2016;12:399–406.

[22] Spielberger C. Manual for the State-Trait Anxiety Inventory. 1983.

[23] Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Arthritis Care Res (Hoboken) 2011:S467-72.

[24] Knight RG, Waal-Manning HJ, Spears GF. Some norms and reliability data for the State-Trait Anxiety Inventory and the Zung Self-Rating Depression scale. Br J Clin Psychol 1983;22:245–9.

[25] McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: Third report of the DLB consortium. Neurology 2005;65:1863–72.

[26] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. (Available from URL Http//www.ohri.ca/programs/clinical_epidemiology/oxford.asp) 2012:2012.

[27] Jelic V, Kivipelto M, Winblad B. Clinical trials in mild cognitive impairment: lessons for the future. J Neurol Neurosurg Psychiatry 2006;77:429–38.

[28] Bierman EJM, Comijs HC, Rijmen F, Jonker C, Beekman ATF. Anxiety symptoms and cognitive performance in later life: results from the longitudinal aging study Amsterdam. Aging Ment Health 2008;12:517–23.

[29] Jacob L, Bohlken J, Kostev K. Risk Factors for Mild Cognitive Impairment in German Primary Care Practices. J Alzheimer's Dis 2017;56:379–84.

[30] Kassem AM, Ganguli M, Yaffe K, Hanlon JT, Lopez OL, Wilson JW, et al. Anxiety symptoms and risk of dementia and mild cognitive impairment in the oldest old women. Aging Ment Health 2017:1–9.

[31] Perna G, Iannone G, Alciati A, Caldirola D. Are Anxiety Disorders Associated with Accelerated Aging? A Focus on Neuroprogression. Neural Plast 2016;2016:1–19.

[32] Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925–35.

[33] Davé S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. Pharmacoepidemiol Drug Saf 2009;18:704–7.

[34] Pietrzak RH, Lim YY, Neumeister A, Ames D, Ellis KA, Harrington K, et al. Amyloid-β, anxiety, and cognitive decline in preclinical Alzheimer disease: a multicenter, prospective cohort study. JAMA Psychiatry 2015;72:284–91.

[35] Fontanella CA, Campo J V., Phillips GS, Hiance-Steelesmith DL, Sweeney HA, Tam K, et al. Benzodiazepine Use and Risk of Mortality Among Patients With Schizophrenia. J Clin Psychiatry 2016;77:661–7.

[36] Orgeta V, Qazi A, Spector AE, Orrell M. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment. In: Orgeta V, editor. Cochrane Database Syst. Rev., Chichester, UK: John Wiley & Sons, Ltd; 2014.

[37] Khoury B, Lecomte T, Fortin G, Masse M, Therien P, Bouchard V, et al. Mindfulness-based therapy: A comprehensive meta-analysis. Clin Psychol Rev 2013;33:763–71.

Figure 1 Flowchart of the search and study selection process; * = manually identified from Petkus et al. (2016)

Table 1 Study Characteristics

	Study type and setting; location	Follow-up/ Look back period; years (SD)	Mean age years (SD)	Female n (%)	Education level; no. (%)	Drop-out rate/Non-response rate %	Baseline cognition measure	Anxiety measure; cut-off	Baseline anxiety, %	Controls for depression; baseline depression measure	Dementia diagnosis; criteria (no. cases); OR/HR (95% CI)
Boot et al. 2013 (n=441)	Population based matched case-controlled, Mayo Clinic Rochester, Minnesota, USA	Lifelong diagnoses documented by medical record	72.5 (7.3) – DLB cases age at diagnosis	103 (23.1)	>9 yrs education; (95)	NR	NR	Clinical diagnosis, present in medical history section of medical record	23, 27% cases; 14, 5% controls	Yes; clinical diagnosis from medical history record	DLB diagnosis by behavioural neurologist; published criteria by McKeith et al (2005) (n=147); OR 7.4 (3.5-16)
Gallacher et al. 2009 (n=1160)	Prospective, community based cohort; Caerphilly, Wales, UK	Mean follow up period; 17.3 (1.3)	56.1 (4.4) – mean age at inclusion	0	no qualifications; 601 (55)	20	NR; dementia unlikely at inclusion (mean age <60 yrs)	STAI; score of ≥35	585, 50%	Yes; GHQ-30	Dementia diagnosis; DSM-IV or medical records (n=90); OR 1.62 (0.59-4.41)
Petkus et al. 2016 (n=1082)	Prospective, community based cohort; Swedish twins drawn from Swedish Twin Registry, Sweden	Follow up period; 28 (0)	60.86 (11.15) – mean age at inclusion	612 (56.6)	Beyond elementary education; 423 (39)	29.8	MMSE	State anxiety subscale of STPI; STPI > 1 SD Q1-Q4 (assessments over 4 time-points)	403, 37%	Yes; OARS depression subscale, CES-D	Dementia diagnosis; DSM-III or DMS-IV (n=172); HR 1.48 (1.01-2.18)
Zilkens et al. 2014 (n=27136)	Population based matched case-controlled, Western Australia	Mean look back period; cases 20.4 (10.4), controls 20.0 (10.3)	78.7 (4.7) – mean age at final time point	15359 (56.6)	NR	6.17 (excluded individuals)	NR	Clinical diagnosis using ICD-10 AM (Australian Modification) codes documented in health records; meeting diagnostic threshold	379, 2.8% cases	Yes; clinical diagnosis by GP	Dementia diagnosis; ICD-10 (n=13568); OR 1.61 (1.28-2.02) (>10 years look back period)

(CES-D = Centre of Epidemiological Studies depression subscale, DLB = Dementia with Lewy bodies, GHQ-30 = 30-item general health questionnaire, NR = not recorded; OARS = older American resources and services; STAI = State trait anxiety inventory; STPI = State trait personality inventory)

Table 2 Case controlled studies: Newcastle-Ottawa scale for assessment of quality of included case controlled studies (+ / - represents whether individual criterion within the subsection was fulfilled)

	Acceptable Criteria	**Zilkens et al. 2014**		**Boot et al. 2013**	
Selection					
Case definition	With independent validation	Record linkage from Western Australian Data Linkage System and Death Registry, no independent validation	-	Assessment for DLB using behavioural neurologist	+
Representative-ness of cases	Consecutive or representative series of cases	All dementia cases in period 2000-2009 identified via read-code; lower limit index dementia age 65 years, upper limit 84 years; dementia in other diseases excluded	+	Recruited from longitudinal studies in period 1984-2013 (Alzheimer Disease Patient Registry, Alzheimer Disease Research Centre Study, and Mayo Clinic Study of Ageing); community dwelling persons aged 70-89 years; excluded structural brain lesions	+
Selection of controls	Community controls	Population controls; randomly selected from electoral role aged ≥65 years prior to extraction of health data for controls	+	Community controls from longitudinal study of ageing; individuals aged ≥65 years; selected if seen by physician in same month as clinical subject diagnosed; matched by age and sex	+
Definition of controls	No history of disease	Excluded if dementia read-code in records; no independent screening	+	Excluded if diagnosed with DLB/AD during the study, previous stroke, head injury, neurologic disease or movement disorder; extensive cognitive and medical examination	+
Comparability					
Comparability of cases and controls on basis of design and analysis	Study controls for the most important factor (+/-), and any additional factor (+/-)	Controls for age, sex, vascular risk factors (diabetes, IHD, AF, CVD, hypertension, hyperlipidaemia, heart failure and past or current smoking), head injury, alcohol dependence syndrome, and depression	+ +	Controls for age, sex; multivariate analyses control for family history, depression, APOE ε4 alleles, education level, head injury, cancer, and vascular risk factors (stroke, diabetes, alcohol, smoking)	+ +
Exposure					
Ascertainment of exposure	Secure record, structured interview by healthcare practitioner	Secure administrative health record, read-codes for mid-life factors documented between aged 30-65 years within years 1966-2009	+	Anxiety history from medical history section of medical record	+
Same method of ascertainment for cases and controls	Yes	Yes; review of risk factor read-codes	+	Yes; review of medical history	+
Non-response rate	Similar for both cases and controls	NR	-	NR	-
Total Score			**7**		**8**

(DLB = Dementia with Lewy bodies; NR = not recorded)

Table 3 Cohort studies: Newcastle-Ottawa scale for assessment of quality of included cohort studies (+ / - represents whether individual criterion within the subsection was fulfilled)

	Acceptable Criteria	Petkus et al. 2016		Gallacher et al. 2009	
Selection					
Representative ness of exposed cohort	Representative of average adult in the community (age/sex)	Population based Swedish twin registry, subsample of twins aged ≥ 50 years	+	Men only, representative of male inhabitants of Caerphilly region	-
Selection of non-exposed cohort	Drawn from same community as exposed cohort	Drawn from same community as exposed cohort	+	Drawn from same community as exposed cohort	+
Ascertainment of exposure	Secured records, clinical diagnosis using diagnostic tools (ICD-10/DSM-V)	State anxiety subscale of the State-Trait Personality Inventory (STPI), containing a subset of items from the STAI	+	Structured interview using STAI	+
Demonstration that outcome of interest was not present at start of study	Assessment for dementia at initial enrolment	No baseline screening, exclusion if previous dementia diagnosis, age at inclusion (mean age 60.86 years) makes cognitive impairment unlikely	-	Age at inclusion (mean age 56.1 years) makes cognitive impairment unlikely	-
Comparability					
Comparability of cohorts on basis of design or analysis	Study controls for the most important factor (+), and for any additional factor (+)	Multivariate models control for depression symptoms, baseline age, sex, education, physical illness	+ +	Study controls for age, social class, marital status, vascular risk factors (alcohol consumption, BP, BMI, total cholesterol, previous vascular disease), educational ability (National Adult Reading Test), and depression symptoms (GHQ-30)	+ +
Exposure					
Assessment of outcome	Independent blind assessment, record linkage	Screening for dementia using MMSE, cognitive in-person testing (assessing a range of cognitive domains), DSM-III or IV, and record linkage using National Patient Registry and National Patient Cause of Death Registry	+	Cognitive function assessed using CAMDEX, FAB, CDR; diagnosis made using DSM-IV, screening of primary care and hospital records	+
Follow up adequate for outcome to occur	Follow up >10 years	28 years	+	>20 years	+
Adequacy of follow up of cohorts	Complete follow up, or subjects lost to follow-up unlikely to introduce bias	NR	-	20% lost to follow up	+
Total Score			**7**		**7**

(BMI = body mass index; BP = blood pressure; CAMDEX = Cambridge mental disorders of the elderly examination; CDR = clinical dementia rating; DSM III/IV/V = Diagnostic and statistical manual of mental disorders III/IV/V; FAB = frontal assessment battery; GHQ-30 = 30-item general health questionnaire; ICD-10 = International classification of diseases 10; MMSE = mini mental state examination; NR = not recorded; STAI = State trait anxiety inventory)

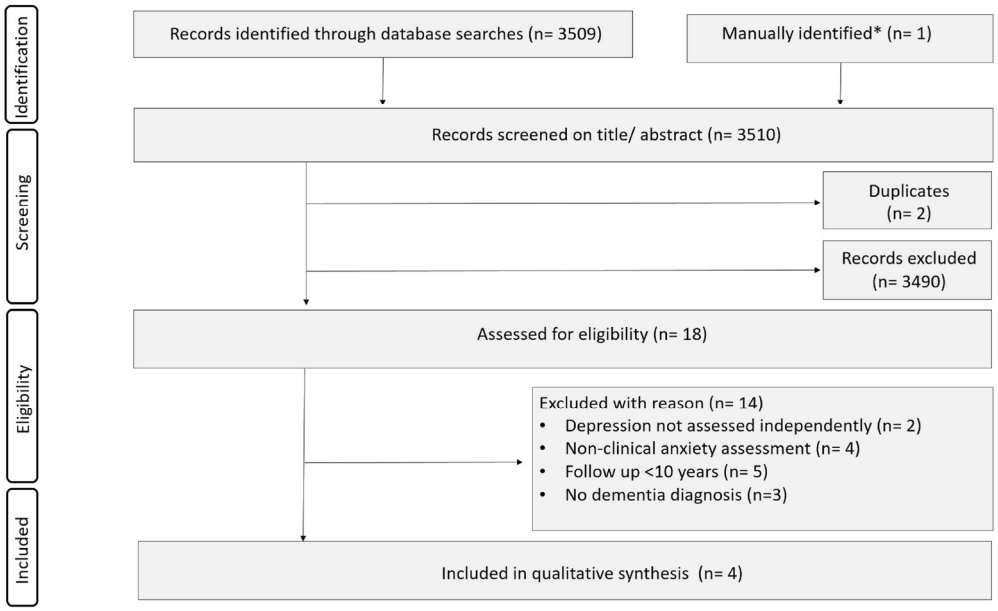

Figure 1 Flowchart of the search and study selection process; * = manually identified from Petkus et al. (2016)

175x106mm (300 x 300 DPI)

Example Search Strategy

Search carried out in Ovid MEDLINE(R) from 1946 to October Week 3 2017

#	Searches	Results
1	dement*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	101878
2	limit 1 to (english language and humans)	84635
3	alzheimer*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	123908
4	limit 3 to (english language and humans)	98174
5	mild cognitive impairment.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	10469
6	limit 5 to (english language and humans)	9789
7	MCI.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	12968
8	limit 7 to (english language and humans)	10517
9	2 OR 4 OR 6 OR 8	155363
10	anx*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	196896
11	limit 10 to (english language and humans)	154215
12	generalised anxiety disorder.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	475
13	limit 12 to (english language and humans)	438
14	GAD.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	7550
15	limit 14 to (english language and humans)	4299
16	11 OR 13 OR 15	156261
17	risk*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	2086806
18	limit 17 to (english language and humans)	1757965
19	odds.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	268449
20	limit 19 to (english language and humans)	257505
21	18 OR 20	1849508
22	9 AND 16 AND 21	776

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2, 9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7,17
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6,7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10,19,20
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10,19,20
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8,9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12,13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11,12,13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Support for mid-life anxiety diagnosis as an independent risk factor for dementia: a systematic review.

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Support for mid-life anxiety diagnosis as an independent risk factor for dementia: a systematic review.

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Abstract

Objectives: Anxiety is an increasingly recognised predictor of cognitive deterioration in older adults and those with mild cognitive impairment (MCI). Often believed to be a prodromal feature of neurodegenerative disease, anxiety may also be an independent risk factor for dementia, operationally defined here as preceding dementia diagnosis by >10 years.

Design: A systematic review of the literature on anxiety diagnosis and long-term risk for dementia was performed following published guidelines.

Setting and participants: MEDLINE, PSYCINFO, and EMBASE were searched for peer-reviewed journals up until 8 March 2017. Publications reporting hazard/odds ratios for all-cause dementia based on clinical criteria from prospective cohort or case-control studies were selected. Included studies measured clinically significant anxiety in isolation or after controlling for symptoms of depression, and reported a mean interval between anxiety assessment and dementia diagnosis of at least 10 years. Methodological quality assessments were performed using the Newcastle-Ottawa scale.

Outcome measure: HR/ORs for all cause dementia.

Results Searches yielded 3510 articles, of which four (0.02%) were eligible. The studies had a combined sample size of 29,819, and all studies found a positive association between clinically significant anxiety and future dementia. Due to the heterogeneity between studies, a meta-analysis was not conducted.

Conclusions Clinically significant anxiety in mid-life was associated with an increased risk of dementia over an interval of at least 10 years. These findings indicate that anxiety may be a risk factor for late-life dementia, excluding anxiety that is related to prodromal cognitive decline. With increasing focus on identifying modifiable risk factors for dementia, more high

quality prospective studies are required to clarify whether clinical anxiety is a risk factor for dementia, separate from a prodromal symptom.

Strengths and limitations of this study:

- This systematic review used a rigorous methodology, with broad search terms and precisely pre-defined inclusion and exclusion criteria to investigate a life-course association between a potentially modifiable risk factor, anxiety, and dementia, whilst excluding anxiety related to pre-clinical dementia.
- Strict exclusion criteria were used to remove studies that did not either discuss anxiety diagnosis alone or control for depression, to account for high levels of anxiety-depression comorbidity
- Study quality was formally investigated using the Newcastle-Ottawa scale
- The review was limited by the lack of assessment of cognition at baseline in retrospective studies, however, the length of look-back minimises the likelihood of cognitive impairment at baseline
- The small number and heterogeneity of study designs rendered a meta-analysis inappropriate, therefore formal statistical analyses could not be performed

Introduction

Dementia, and more specifically Alzheimer's disease (AD), is a progressive neurocognitive disease. In the absence of any disease modifying treatments, there is increasing focus on primary prevention to reduce risk of its development, and on early intervention to potentially slow progression. A better understanding of risk factors for dementia is therefore vital for improving therapeutic interventions. Alongside a number of well

described cardiovascular risk factors [1], increasing evidence has highlighted the association between psychiatric illnesses and the development of late-onset dementia [2]. Further work is needed to understand whether these psychiatric symptoms and illnesses represent prodromal symptoms or act as independent risk factors.

Depression has been consistently related to the development of dementia [3]. Three meta-analyses have reported that a diagnosis of depression is associated with up to a twofold increase in risk [3–5]. Ownby and colleagues further report that a longer interval between diagnosis of depression and diagnosis of dementia is significantly associated with an increased odds ratio (OR) of developing dementia [3]. This substantiates interpretations of depression as a risk factor for developing dementia, whereas a stronger association over shorter intervals would have been more indicative of prodromal symptoms. Conversely, a recent study found no association between dementia and depressive symptoms experienced more than 22 years before dementia diagnosis, however a positive association between dementia and depressive symptoms experienced on average 11 years prior to diagnosis of dementia was reported [6].

Although anxiety is a prevalent psychiatric disorder [7], and commonly co-occurs with depression, the impact of anxiety on risk for cognitive decline and dementia has been far less studied. Anxiety symptoms are commonly experienced in the years preceding a dementia diagnosis [8], and have been associated with cognitive decline and the progression from MCI to AD [9–11]. A recent review reported that anxiety and neuropsychiatric symptoms not reaching clinically diagnostic levels were associated with increased risk of dementia [12]. The authors indicated that anxiety was likely a prodromal symptom of dementia in these community samples. This may well have been the case,

particularly given the relatively short intervals between assessment of anxiety symptoms and assessment of dementia, however, this does not preclude anxiety also being a risk factor.

The association between anxiety symptoms (independent of the dementia-prodrome) and dementia in later life could more easily be investigated with longer intervals between anxiety assessment and dementia diagnosis, as the studies that have investigated this association within a 5-10 year interval have reported variable results [13,14]. The average length of prodromal preclinical cognitive decline has been proposed to be between 5-6 years [15], and individuals diagnosed with MCI may progress to AD within 5 years [16]. Therefore, examining studies with at least a 10-year interval between anxiety assessment and dementia diagnosis would increase likelihood that anxiety is independent from the dementia prodrome.

It is possible that anxiety symptoms meeting diagnostic threshold will have a stronger association with dementia than general symptoms because this has been shown with depression [4]. To date, there has been no systematic review to investigate the association between clinically significant anxiety and dementia. The aim of this study was therefore to review the literature examining the association between clinically significant levels of anxiety and dementia risk over a longer timescale (>10 years).

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care [17].

Search strategy

A systematic literature search of MEDLINE, PSYCINFO and EMBASE databases was conducted of articles published from inception up until 8th March 2017 to identify articles reporting analyses of the association between anxiety (as defined by clinical diagnosis or self-report scales with a clinically significant threshold) and dementia or MCI incidence. Search terms used consisted of: (dement* OR Alzheimer* OR "mild cognitive impairment" OR MCI) AND (anx* OR "generalised anxiety disorder" OR GAD) AND (risk* OR odds), as presented in online supplementary table ST1. We aimed to identify articles discussing (1) diagnosis of any type of dementia, (2) anxiety diagnosis, and (3) risk of dementia. The search was restricted to human studies and those published in English. Reference lists were searched for additional relevant articles. Searches were conducted by a single reviewer (AG). An independent review of all screened articles was conducted by a second reviewer (MS). Any disagreement was resolved by consensus with a third reviewer (NM), which occurred in two cases.

Selection Criteria and Article Screening

Inclusion criteria were 1) a diagnosis of anxiety or an assessment of anxiety symptoms meeting diagnostic criteria using a standardised assessment tool, excluding populations with post-traumatic stress disorder (PTSD) or obsessive-compulsive disorder (OCD); 2) population-based studies where anxiety is assessed at least – on average – 10 years preceding final clinical assessment for dementia in line with previous meta-analyses on depression using intervals of at least 10 years [3]; 3) a diagnosis of dementia using validated criteria (e.g. Diagnostic Statistical Manual III-IV (DSM III-IV), International Classification of Diseases 10 (ICD-10)); 4) late-onset dementia diagnoses (aged ≥65 years). Eligible articles were identified by performing an initial screen of titles and abstracts, followed by a full

article review of those that passed screening. All retrospective and prospective studies that met these criteria were selected.

Data extraction

Outcome measures related to anxiety and dementia diagnosis were independently extracted by two authors (AG, MS). Disagreements were resolved through discussion. Study design, sample characteristics (including educational level and age), follow-up length, dropout rate, anxiety (including measure and baseline score where appropriate), criteria for assessing dementia, and measurements of depression as a confounder (including measure and baseline score), were recorded. In cases of insufficient data, authors were contacted by email.

INSERT FIGURE 1

Study Quality

Two authors (AG, MS) independently assessed study quality and risk of bias using the Newcastle-Ottawa scale, which contains separate quality assessment instruments for case-control and cohort studies.

Results

Literature Search

The literature search detected 3509 citations, of which two were duplicates. One further paper was identified manually during reference screening. After screening titles and abstracts, 18 full-text articles were assessed for eligibility. Fourteen articles were excluded based on criteria described earlier (Figure 1), four studies were included in the final review [18–21].

Study Characteristics

Characteristics of the four selected studies are shown in Table 1. Clinically significant anxiety was documented based on clinical diagnosis using International Classification of Diseases 10 (ICD-10) criteria (n = 2), the State Trait Anxiety Inventory (STAI, n = 1) and a subscale of the State Trait Personality Inventory (STPI, n = 1).

Gallacher et al. (2009) measured anxiety using the STAI, which has a range from 20 to 80 [22], and is a validated measure for assessing anxiety symptoms. A clinically significant cut-off of 39-40 has been proposed [23,24]. Gallacher et al. (2009) categorised 'high anxiety' as having a STAI score between 35 and 72, compared to a 'low anxiety' group who had a STAI score between 20 and 34. Boot et al. (2013) and Zilkens et al. (2014) used ICD-10 criteria to diagnose an anxiety disorder.

Petkus et al. (2016) assessed anxiety using state anxiety subscale of the State-Trait Personality Inventory (STPI), which contains a subset of items from the STAI. Participants scoring at least one standard deviation above the population mean, equating to a score of ≥25 out of 40, were categorised having 'high anxiety'**.** Although there is no established cut-off for clinically significant anxiety using this scale, scores greater than 1 SD above the population mean are likely to represent a group with a high anxiety symptom burden. After discussion amongst the reviewers (AG, MS, NLM), we reached a consensus judgement that the study was suitable for inclusion in this review.

Dementia diagnosis was in most cases assessed using DSM III-IV (n = 2) or ICD-10 criteria (n = 1), although the study by Boot et al. (2013) assessed Dementia with Lewy Bodies (DLB) by clinical diagnosis using published criteria [25].

Sample sizes of the studies ranged from 441 to 27 136 participants, recruited from both or either community and hospital inpatient/outpatient populations. Gallacher et al. (2009) and Petkus et al. (2016) conducted prospective cohort studies using a community twin-population that excluded dementia at baseline. Zilkens et al. (2014), and Boot et al. (2013) conducted matched case-control studies, which retrospectively analysed community and hospital records of individuals with dementia or case-matched controls for anxiety diagnosis and therefore did not include a cognitive assessment at baseline to exclude dementia. Zilkens et al. (2014) drew controls from the electoral roll, whereas Boot et al. (2013) drew them from the community-dwelling persons included in the Mayo Clinic Study of Aging. The proportion of females in each study ranged from 0 to 56.6%. Educational level was recorded for all but one study; which ranged from 55% with no qualifications to 95% with >9 years of education.

INSERT TABLE 1

Anxiety diagnosis association with dementia

All studies included in this review found a significant increase in the number of dementia diagnoses in patients who had a clinical anxiety diagnosis or experienced clinically significant anxiety symptoms on average at least 10 years prior to their diagnosis of dementia; Zilkens et al. (2014): OR = 1.61 (95% CI 1.28-2.02), Boot et al. (2013): OR = 7.4 (95% CI 3.5-16), Gallacher et al. (2009): OR = 1.62 (95% CI 0.59-4.41) and Petkus et al. (2016): OR = 1.48 (95% CI 1.01-2.18), respectively [18–21]. On the whole, retrospective studies that looked back for life-long diagnoses of anxiety found a stronger association between mid-life anxiety and later dementia diagnosis, than prospective studies investigating an association over a shorter time period. Additionally, Petkus et al. (2016) demonstrated that the association

between high anxiety and dementia diagnosis remained when they excluded participants who developed dementia within 5 years of the baseline assessment. This subsample had an average interval between baseline and dementia diagnosis of 14.7 years (SD 6.7 years). Both lend support that the associations found were independent of prodromal dementia symptoms.

Each study controlled for a range of demographic factors, with all controlling for vascular and other psychiatric risk factors (Table 2 and 3). All studies assessed and controlled for depression symptoms in their analysis. Boot et al. (2013) found a stronger association between anxiety diagnosis alone with future dementia than either depression diagnosis alone or mixed anxiety and depression diagnosis, although the number of individuals with anxiety was markedly larger than those in the other two categories (anxiety alone n=168; depression alone n=52; anxiety and depression n=56). Although Zilkens et al. (2014) assessed a range of psychiatric diagnoses including anxiety and depression, they did not assess their interaction. Petkus et al. (2016) and Gallacher et al. (2009), whilst controlling for depression, made no assessment of the comparative strength of relationship or their interaction.

Study Quality Rating

All studies included were rated highly on the Newcastle-Ottawa scale [26]. From a maximum score of 9, Boot et al (2013) was rated 8; and Zilkens et al. (2014), Petkus et al. (2016) and Gallacher et al. (2009) were each rated 7. These studies were of similar quality to those included in a recent meta-analysis examining dementia risk estimates associated with late-life depression [4].

Three of the studies had representative samples of community populations; the fourth led by Gallacher et al. (2009) included only men. All controlled for a range of both demographic, physical and psychological health factors. All outcomes were assessed either via secure health records, or independent validation. Gallacher et al. (2009) experienced 20% loss to follow-up, which compares favourably to the pre-mentioned Cherbuin et al. (2015) review, which considered studies with an attrition rate of between 4.3% and 55.46%, and a review of MCI drug studies with attrition rates varying from 12% to 49% [27]. Petkus et al. (2016) did not clearly report loss to follow-up. For both case-control studies, the primary care records did not include a cognitive assessment at baseline. Therefore, pre-existing cognitive impairment before diagnosis cannot be ruled out, although long look-back periods make this less likely.

INSERT TABLE 2

INSERT TABLE 3

Discussion

This systematic review found four high quality studies that all showed a positive association between clinically significant anxiety and risk of late-onset dementia over a mean interval of at least 10 years from anxiety assessment to dementia diagnosis, even after accounting for potential confounders. This important finding provides further evidence that a common mental health condition in mid-life is associated with later life neurodegenerative disorders.

Anxiety symptomatology has previously been related to dementia risk and cognitive decline, although not conclusively [10,28]. A recent systematic review reported a positive association between anxiety symptoms and dementia diagnosis over a short time interval [12]. In that review the majority of studies reported follow up periods between 2-3.8 years.

A single study had a follow up time of up to 11.8 years, however the average interval between anxiety and dementia diagnosis may have been less than 10 years, therefore it was not included in the current review [13]. Gulpers et al. found stronger associations with smaller intervals between assessment of anxiety and dementia diagnosis. As a result, the authors concluded that anxiety may result from a prodromal state of dementia, where an increase in anxiety may be due to an individual's insight into their early, subjective experience of cognitive decline [12]. Given the short time interval between assessments, Gulpers et al. were unable to determine whether anxiety could also serve as an independent risk for dementia. This review reports solely articles that were not included Gulpers et al.'s analyses, and therefore furthers their work by providing an independent assessment of the anxiety-dementia association. Effect sizes of the studies included in this review (1.48 - 7.4) were comparable to the overall effect size found by Gulpers et al. (2016) of 1.61, suggesting that the association between clinically significant mid-life anxiety and later-life dementia is as strong as that between late-life anxiety symptoms and dementia.

The prodromal phase of dementia can begin several years before objective dementia is manifest. In the present review, we sought to minimise the potential influence of pre-clinical cognitive decline by including only studies that assessed anxiety and dementia diagnoses over an extended period. Three studies (Zilkens et al. 2014; Gallacher et al. 2009; Petkus et al. 2016) demonstrated a mean interval of at least 10 years between the anxiety and dementia evaluations. Boot et al. (2013) analysed participant's lifelong medical record, however, the mean interval between anxiety and dementia diagnosis was not reported.

Findings from this review corroborate recent evidence that anxiety symptoms or diagnosis are associated with risk of MCI [29,30]. These findings further complement the association

between depression and dementia diagnosis [4], which is particularly relevant due to high levels of anxiety-depression comorbidity. Moreover, they lend support for the proposal that multiple psychiatric risk factors are implicated together as a latent risk factor for dementia [2].

It has recently been suggested that a longer interval period between anxiety and dementia diagnosis may provide evidence for a common biological pathway linking anxiety, depression, and dementia [20]. An abnormal stress response, such as exhibited in anxiety disorders, may be associated with accelerated cellular ageing and neuro-progression (a pathological reorganisation of the central nervous system) resulting in increased neurodegeneration, neuronal apoptosis and lowered neuroplasticity [31]. Although glucocorticoid, inflammatory mediator and vascular disease mechanisms are hypothesised [3,32], as yet, no convincing candidate biological mechanism linking anxiety and cognitive impairment exists.

The results of this review should be interpreted in the light of their limitations. Only studies that had been published and written in English were included, which may limit extrapolation across broader populations. Retrospective studies did not examine baseline cognition and therefore cannot exclude early cognitive decline at the time of anxiety assessment, however, the length of look-back, ranging from over 10 years to the first entry of an individual's medical record, minimises the likelihood of cognitive impairment at baseline. To account for high levels of anxiety-depression comorbidity, this review included only papers discussing anxiety diagnosis alone, or those that controlled for depression symptomatology. However, the Zilkens et al. (2014) and Boot et al. (2013) cannot completely exclude overlap of these two commonly comorbid illnesses because their occurrence was ascertained from

lists of diagnoses in medical records. The use of read codes in retrospective studies may have resulted in lower identification of individuals with clinically significant anxiety as a result of inconsistent entry of read codes during evaluations, or of absence of clinical record for non-help seekers [33]. Publication bias may also have influenced the studies included, as positive findings may be more likely to have been published than studies finding no association. Furthermore, results must be interpreted in the light of proposals that the prodromal AD pathophysiologic processes may develop beyond 10 years before the onset of clinical symptoms [34].

Whether reducing anxiety in middle-age would result in reduced risk of dementia remains an open question. The effect of treatment of anxiety using pharmacologic and non-pharmacologic therapies during midlife on later risk for dementia has not yet been investigated. Benzodiazepines, commonly used in the treatment of anxiety, have been shown to increase risk of mortality in some groups [35], and therefore cannot be considered a measure to reduce dementia incidence in those with clinical anxiety. It is possible that diverse non-pharmacological therapies, including talking therapies [36] and mindfulness-based interventions and meditation practices [37], that are known to reduce anxiety in midlife, could have a risk-reducing effect, although this is yet to be thoroughly researched.

Given the high prevalence of anxiety seen in primary care, we suggest that general practitioners could consider anxiety alongside depression as an indicator of risk factor for dementia. To improve the rate of earlier diagnosis of dementia, close monitoring of subtle cognitive decline in older adults with a history of anxiety, depression and cerebrovascular disease would be encouraged. This review expands our understanding of anxiety as a potentially modifiable risk for dementia. Given the limited number of studies investigating

the anxiety-dementia relationship, further research is required to assess underlying mechanisms that link these disorders, and to disambiguate anxiety's potential role as a risk factor as separate from a prodromal symptom of dementia.

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Contributors

AG contributed to design of the study, data screening and extraction, drafting of the manuscript and submission. MS contributed to literature search, data screening and extraction, and manuscript preparation. JDH contributed to the study design, provided methodological expertise and editing of the manuscript. NLM contributed to the conception and study design, data interpretation, and editing of the manuscript.

Competing interests

None of the contributing authors have any conflicting interests to declare.

Data sharing statement

No additional data are available.

References

[1] Fillit H, Nash D, Rundek T, Zuckerman A. Cardiovascular risk factors and dementia. Am J Geriatr Pharmacother 2008;6:100–18.

[2] Marchant NL, Howard RJ. Cognitive debt and Alzheimer's disease. J Alzheimers Dis 2015;44:755–70.

[3] Ownby R, Crocco E, Acevedo A, John V, Loewenstein D. Depression and Risk for Alzheimer Disease: a systematic review, meta-analysis and metaregression analysis. Arch Gen Psychiatry 2006;63:530.

[4] Cherbuin N, Kim S, Anstey KJ. Dementia risk estimates associated with measures of depression: a systematic review and meta-analysis. BMJ Open 2015;5:e008853.

[5] Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF, Byers A, et al. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry 2013;202:329–35.

[6] Singh-Manoux A, Dugravot A, Fournier A, Abell J, Ebmeier K, Kivimäki M, et al. Trajectories of Depressive Symptoms Before Diagnosis of Dementia. JAMA Psychiatry 2017;74:712.

[7] Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci 2015;17:327–35.

[8] Gallagher D, Coen R, Kilroy D, Belinski K, Bruce I, Coakley D, et al. Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. Int J Geriatr Psychiatry 2011;26:166–72.

[9] Palmer K, Berger AK, Monastero R, Winblad B, Backman L, Fratiglioni L. Predictors of progression from mild cognitive impairment to Alzheimer disease. Neurology 2007;68:1596–602.

[10] Yochim BP, Mueller AE, Segal DL. Late life anxiety is associated with decreased memory and executive functioning in community dwelling older adults. J Anxiety Disord 2013;27:567–75.

[11] Beaudreau SA, O'Hara R. Late-life anxiety and cognitive impairment: a review. Am J Geriatr Psychiatry 2008;16:790–803.

[12] Gulpers B, Ramakers I, Hamel R, Kohler S, Voshaar R, Verhey F. Anxiety as a Predictor for Cognitive Decline and Dementia: A Systematic Review and Meta-analysis. Am J Geriatr Psychiatry 2016.

[13] de Bruijn RFAG, Direk N, Mirza SS, Hofman A, Koudstaal PJ, Tiemeier H, et al. Anxiety is not associated with the risk of dementia or cognitive decline: the Rotterdam Study. Am J Geriatr Psychiatry 2014;22:1382–90.

[14] Burton C, Campbell P, Jordan K, Strauss V, Mallen C. The association of anxiety and depression with future dementia diagnosis: A case-control study in primary care. Fam Pract 2013;30:25–30.

[15] Wilson RS, Leurgans SE, Boyle PA, Bennett DA. Cognitive decline in prodromal

Alzheimer disease and mild cognitive impairment. Arch Neurol 2011;68:351–6.

[16] Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. Lancet 2006;367:1262–70.

[17] Centre for Reviews and Dissemination. CRD's Guidance for undertaking reviews in health care. 2009.

[18] Zilkens RR, Bruce DG, Duke J, Spilsbury K, Semmens JB. Severe psychiatric disorders in mid-life and risk of dementia in late-life (age 65-84 years): A population based case-control study. Curr Alzheimer Res 2014;11:681–93.

[19] Boot BP, Orr CF, Ahlskog JE, Ferman TJ, Roberts R, Pankratz VS, et al. Risk factors for dementia with Lewy bodies: a case-control study. Neurology 2013;81:833–40.

[20] Gallacher J, Bayer A, Fish M, Pickering J, Pedro S, Dunstan F, et al. Does anxiety affect risk of dementia? Findings from the Caerphilly Prospective Study. Psychosom Med 2009;71:659–66.

[21] Petkus AJ, Reynolds CA, Wetherell JL, Kremen WS, Pedersen NL, Gatz M, et al. Anxiety is associated with increased risk of dementia in older Swedish twins. Alzheimer's Dement 2016;12:399–406.

[22] Spielberger C. Manual for the State-Trait Anxiety Inventory. 1983.

[23] Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Arthritis Care Res (Hoboken) 2011:S467-72.

[24] Knight RG, Waal-Manning HJ, Spears GF. Some norms and reliability data for the State-Trait Anxiety Inventory and the Zung Self-Rating Depression scale. Br J Clin Psychol 1983;22:245–9.

[25] McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: Third report of the DLB consortium. Neurology 2005;65:1863–72.

[26] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. (Available from URL Http//www.ohri.ca/programs/clinical_epidemiology/oxford.asp) 2012:2012.

[27] Jelic V, Kivipelto M, Winblad B. Clinical trials in mild cognitive impairment: lessons for the future. J Neurol Neurosurg Psychiatry 2006;77:429–38.

[28] Bierman EJM, Comijs HC, Rijmen F, Jonker C, Beekman ATF. Anxiety symptoms and cognitive performance in later life: results from the longitudinal aging study Amsterdam. Aging Ment Health 2008;12:517–23.

[29] Jacob L, Bohlken J, Kostev K. Risk Factors for Mild Cognitive Impairment in German Primary Care Practices. J Alzheimer's Dis 2017;56:379–84.

[30] Kassem AM, Ganguli M, Yaffe K, Hanlon JT, Lopez OL, Wilson JW, et al. Anxiety symptoms and risk of dementia and mild cognitive impairment in the oldest old women. Aging Ment Health 2017:1–9.

[31] Perna G, Iannone G, Alciati A, Caldirola D. Are Anxiety Disorders Associated with Accelerated Aging? A Focus on Neuroprogression. Neural Plast 2016;2016:1–19.

[32] Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925–35.

[33] Davé S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. Pharmacoepidemiol Drug Saf 2009;18:704–7.

[34] Pietrzak RH, Lim YY, Neumeister A, Ames D, Ellis KA, Harrington K, et al. Amyloid-β, anxiety, and cognitive decline in preclinical Alzheimer disease: a multicenter, prospective cohort study. JAMA Psychiatry 2015;72:284–91.

[35] Fontanella CA, Campo J V., Phillips GS, Hiance-Steelesmith DL, Sweeney HA, Tam K, et al. Benzodiazepine Use and Risk of Mortality Among Patients With Schizophrenia. J Clin Psychiatry 2016;77:661–7.

[36] Orgeta V, Qazi A, Spector AE, Orrell M. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment. In: Orgeta V, editor. Cochrane Database Syst. Rev., Chichester, UK: John Wiley & Sons, Ltd; 2014.

[37] Khoury B, Lecomte T, Fortin G, Masse M, Therien P, Bouchard V, et al. Mindfulness-based therapy: A comprehensive meta-analysis. Clin Psychol Rev 2013;33:763–71.

Figure 1 Flowchart of the search and study selection process; * = manually identified from Petkus et al. (2016)

Table 1 Study Characteristics

	Study type and setting; location	Follow-up/ Look back period; years (SD)	Mean age years (SD)	Female n (%)	Education level; no. (%)	Drop-out rate/Non-response rate %	Baseline cognition measure	Anxiety measure; cut-off	Baseline anxiety, %	Controls for depression; baseline depression measure	Dementia diagnosis; criteria (no. cases); OR/HR (95% CI)
Boot et al. 2013 (n=441)	Population based matched case-controlled, Mayo Clinic Rochester, Minnesota, USA	Lifelong diagnoses documented by medical record	72.5 (7.3) – DLB cases age at diagnosis	103 (23.1)	>9 yrs education; (95)	NR	NR	Clinical diagnosis, present in medical history section of medical record	23, 27% cases; 14, 5% controls	Yes; clinical diagnosis from medical history record	DLB diagnosis by behavioural neurologist; published criteria by McKeith et al (2005) (n=147); OR 7.4 (3.5-16)
Gallacher et al. 2009 (n=1160)	Prospective, community based cohort; Caerphilly, Wales, UK	Mean follow up period; 17.3 (1.3)	56.1 (4.4) – mean age at inclusion	0	no qualifications; 601 (55)	20	NR; dementia unlikely at inclusion (mean age <60 yrs)	STAI; score of ≥35	585, 50%	Yes; GHQ-30	Dementia diagnosis; DSM-IV or medical records (n=90); OR 1.62 (0.59-4.41)
Petkus et al. 2016 (n=1082)	Prospective, community based cohort; Swedish twins drawn from Swedish Twin Registry, Sweden	Follow up period; 28 (0)	60.86 (11.15) – mean age at inclusion	612 (56.6)	Beyond elementary education; 423 (39)	29.8	MMSE	State anxiety subscale of STPI; STPI > 1 SD Q1-Q4 (assessments over 4 time-points)	403, 37%	Yes; OARS depression subscale, CES-D	Dementia diagnosis; DSM-III or DMS-IV (n=172); HR 1.48 (1.01-2.18)
Zilkens et al. 2014 (n=27136)	Population based matched case-controlled, Western Australia	Mean look back period; cases 20.4 (10.4), controls 20.0 (10.3)	78.7 (4.7) – mean age at final time point	15359 (56.6)	NR	6.17 (excluded individuals)	NR	Clinical diagnosis using ICD-10 AM (Australian Modification) codes documented in health records; meeting diagnostic threshold	379, 2.8% cases	Yes; clinical diagnosis by GP	Dementia diagnosis; ICD-10 (n=13568); OR 1.61 (1.28-2.02) (>10 years look back period)

(CES-D = Centre of Epidemiological Studies depression subscale, DLB = Dementia with Lewy bodies, GHQ-30 = 30-item general health questionnaire, NR = not recorded; OARS = older American resources and services; STAI = State trait anxiety inventory; STPI = State trait personality inventory)

Table 2 Case controlled studies: Newcastle-Ottawa scale for assessment of quality of included case controlled studies (+ / - represents whether individual criterion within the subsection was fulfilled)

	Acceptable Criteria	**Zilkens et al. 2014**		**Boot et al. 2013**	
Selection					
Case definition	With independent validation	Record linkage from Western Australian Data Linkage System and Death Registry, no independent validation	-	Assessment for DLB using behavioural neurologist	+
Representative-ness of cases	Consecutive or representative series of cases	All dementia cases in period 2000-2009 identified via read-code; lower limit index dementia age 65 years, upper limit 84 years; dementia in other diseases excluded	+	Recruited from longitudinal studies in period 1984-2013 (Alzheimer Disease Patient Registry, Alzheimer Disease Research Centre Study, and Mayo Clinic Study of Ageing); community dwelling persons aged 70-89 years; excluded structural brain lesions	+
Selection of controls	Community controls	Population controls; randomly selected from electoral role aged ≥65 years prior to extraction of health data for controls	+	Community controls from longitudinal study of ageing; individuals aged ≥65 years; selected if seen by physician in same month as clinical subject diagnosed; matched by age and sex	+
Definition of controls	No history of disease	Excluded if dementia read-code in records; no independent screening	+	Excluded if diagnosed with DLB/AD during the study, previous stroke, head injury, neurologic disease or movement disorder; extensive cognitive and medical examination	+
Comparability					
Comparability of cases and controls on basis of design and analysis	Study controls for the most important factor (+/-), and any additional factor (+/-)	Controls for age, sex, vascular risk factors (diabetes, IHD, AF, CVD, hypertension, hyperlipidaemia, heart failure and past or current smoking), head injury, alcohol dependence syndrome, and depression	+ +	Controls for age, sex; multivariate analyses control for family history, depression, APOE ε4 alleles, education level, head injury, cancer, and vascular risk factors (stroke, diabetes, alcohol, smoking)	+ +
Exposure					
Ascertainment of exposure	Secure record, structured interview by healthcare practitioner	Secure administrative health record, read-codes for mid-life factors documented between aged 30-65 years within years 1966-2009	+	Anxiety history from medical history section of medical record	+
Same method of ascertainment for cases and controls	Yes	Yes; review of risk factor read-codes	+	Yes; review of medical history	+
Non-response rate	Similar for both cases and controls	NR	-	NR	-
Total Score			**7**		**8**

(DLB = Dementia with Lewy bodies; NR = not recorded)

Table 3 Cohort studies: Newcastle-Ottawa scale for assessment of quality of included cohort studies (+ / - represents whether individual criterion within the subsection was fulfilled)

	Acceptable Criteria	Petkus et al. 2016		Gallacher et al. 2009	
Selection					
Representative ness of exposed cohort	Representative of average adult in the community (age/sex)	Population based Swedish twin registry, subsample of twins aged ≥ 50 years	+	Men only, representative of male inhabitants of Caerphilly region	-
Selection of non-exposed cohort	Drawn from same community as exposed cohort	Drawn from same community as exposed cohort	+	Drawn from same community as exposed cohort	+
Ascertainment of exposure	Secured records, clinical diagnosis using diagnostic tools (ICD-10/DSM-V)	State anxiety subscale of the State-Trait Personality Inventory (STPI), containing a subset of items from the STAI	+	Structured interview using STAI	+
Demonstration that outcome of interest was not present at start of study	Assessment for dementia at initial enrolment	No baseline screening, exclusion if previous dementia diagnosis, age at inclusion (mean age 60.86 years) makes cognitive impairment unlikely	-	Age at inclusion (mean age 56.1 years) makes cognitive impairment unlikely	-
Comparability					
Comparability of cohorts on basis of design or analysis	Study controls for the most important factor (+), and for any additional factor (+)	Multivariate models control for depression symptoms, baseline age, sex, education, physical illness	+ +	Study controls for age, social class, marital status, vascular risk factors (alcohol consumption, BP, BMI, total cholesterol, previous vascular disease), educational ability (National Adult Reading Test), and depression symptoms (GHQ-30)	+ +
Exposure					
Assessment of outcome	Independent blind assessment, record linkage	Screening for dementia using MMSE, cognitive in-person testing (assessing a range of cognitive domains), DSM-III or IV, and record linkage using National Patient Registry and National Patient Cause of Death Registry	+	Cognitive function assessed using CAMDEX, FAB, CDR; diagnosis made using DSM-IV, screening of primary care and hospital records	+
Follow up adequate for outcome to occur	Follow up >10 years	28 years	+	>20 years	+
Adequacy of follow up of cohorts	Complete follow up, or subjects lost to follow-up unlikely to introduce bias	NR	-	20% lost to follow up	+
Total Score			**7**		**7**

(BMI = body mass index; BP = blood pressure; CAMDEX = Cambridge mental disorders of the elderly examination; CDR = clinical dementia rating; DSM III/IV/V = Diagnostic and statistical manual of mental disorders III/IV/V; FAB = frontal assessment battery; GHQ-30 = 30-item general health questionnaire; ICD-10 = International classification of diseases 10; MMSE = mini mental state examination; NR = not recorded; STAI = State trait anxiety inventory)

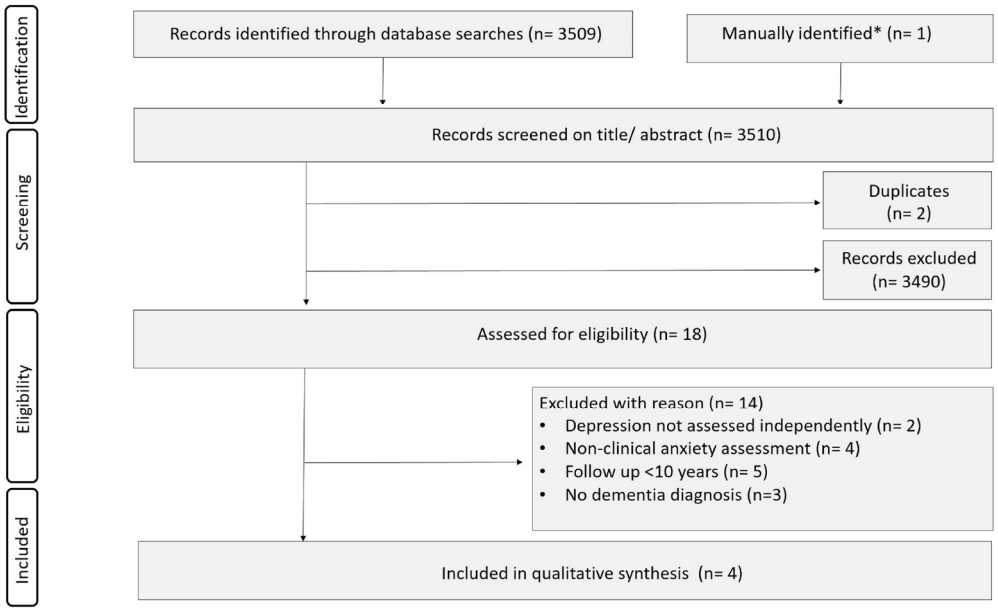

Figure 1 Flowchart of the search and study selection process; * = manually identified from Petkus et al. (2016)

175x106mm (300 x 300 DPI)

Example Search Strategy

Search carried out in Ovid MEDLINE(R) from 1946 to October Week 3 2017

#	Searches	Results
1	dement*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	101878
2	limit 1 to (english language and humans)	84635
3	alzheimer*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	123908
4	limit 3 to (english language and humans)	98174
5	mild cognitive impairment.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	10469
6	limit 5 to (english language and humans)	9789
7	MCI.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	12968
8	limit 7 to (english language and humans)	10517
9	2 OR 4 OR 6 OR 8	155363
10	anx*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	196896
11	limit 10 to (english language and humans)	154215
12	generalised anxiety disorder.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	475
13	limit 12 to (english language and humans)	438
14	GAD.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	7550
15	limit 14 to (english language and humans)	4299
16	11 OR 13 OR 15	156261
17	risk*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	2086806
18	limit 17 to (english language and humans)	1757965
19	odds.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	268449
20	limit 19 to (english language and humans)	257505
21	18 OR 20	1849508
22	9 AND 16 AND 21	776

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2, 9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7,17
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6,7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10,19,20
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10,19,20
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8,9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12,13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11,12,13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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